ANNALS OF
INTERNAL MEDICINE

VOLUME 17 SEPTEMBER, 1942 NUMBER 3

PRIMARY COCCIDIOIDOMYCOSIS: A ROENTGENOGRAPHIC STUDY OF 40 CASES *

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THE occurrence of coccidioidal infection within the human body was first described [1] 50 years ago. For the next 45 years the disease was recognized in only its relatively fatal granulomatous form until Dickson in 1937 [2] established the existence of a benign primary form of the infection. He also suggested the term, Coccidioidomycosis, which would apply to all types of infection produced by *Coccidioides immitis*. He further classified cases as due to primary coccidioidomycosis and to progressive (secondary) or granulomatous coccidioidomycosis. The basis for this distinction was the nondestructive type of reaction produced in the tissues by the first inhalation of the chlamydospores in contrast to the damaging granulomatous changes which develop during progressive secondary disease.

The mode of infection has been shown definitely to occur through the medium of dusty soil containing the chlamydospores of the fungus in its vegetative phase.[3] General opinion in the literature has established that the chief portal of entry is the lungs as would be expected in an inhalation type of disease. Transmission from person to person or animal to animal is unknown.

The prevalence of coccidioidal infection in the vast inland San Joaquin valley of California, with its warm and dry climate, has been described by both Dickson [4] and C. E. Smith.[5] The inhabitants of this area are considered to have become generally infected early in life or within the first year of their coming to the valley. Locally, the disease is recognized when associated with erythema nodosum as "Desert" or "Valley Fever." As the skin rash only occurs in 2 to 5 per cent of the cases of primary infection the majority of the residents are unaware of the actual time that they became infected. Farness [6] has recently pointed out the high incidence of coccidioidal infection in parts of Arizona and has justifiably ventured the opinion

* Read at the St. Paul meeting of the American College of Physicians April 24, 1942.

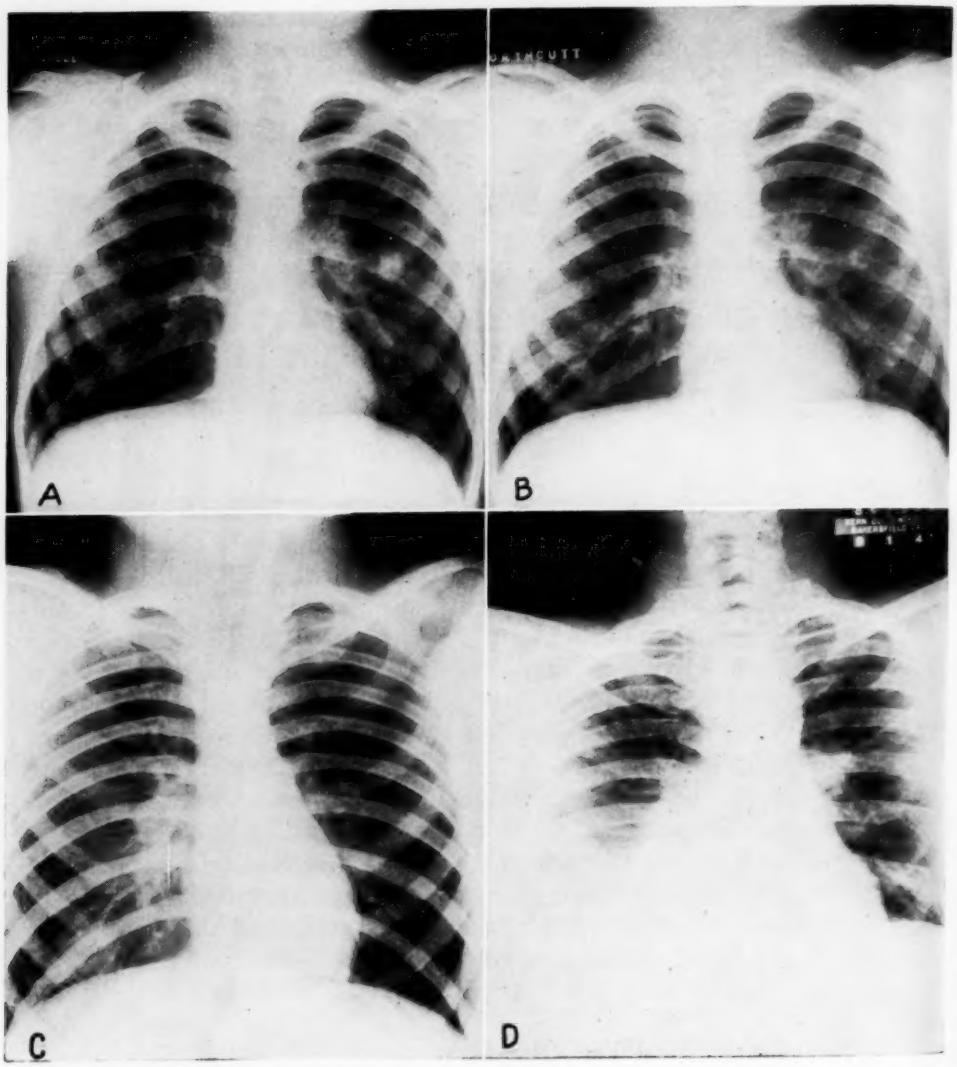

FIG. 1. *A*. Showing soft solitary nodular infiltration outside of left hilus in a 13 year old American boy who came to the San Joaquin Valley from Texas two years ago. Acute illness followed by erythema nodosum 10 days after onset.

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

Negative cutaneous reaction to 0.1 c.c. of 1:100 old tuberculin and PPD second strength.

Serological tests: strongly positive precipitins at first, gradually disappearing with development of a slightly positive complement fixation five weeks later and finally disappearance of all circulating antibodies.

B. (Four months after onset of illness.) Partial clearing of the nodular infiltrate, no evidence of adenopathy. Patient well.

C. Opacity in right base with small area of central clearing and enlargement of right hilus in an 11 year old American boy who developed acute pleurisy and erythema nodosum three months after coming to the San Joaquin Valley. Gastric wash culture positive for *Coccidioides immitis*.

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

Negative cutaneous reaction to 0.1 c.c. of 1:100 old tuberculin.

that the disease probably exists unrecognized in other areas where prevailing dryness of climate and soil conditions are favorable for the growth of the fungus. Shelton [7] describes a new endemic area on the western slope of the Coast Range Mountains of California and the development of coccidioidal infection in 14 of a group of 736 soldiers within three months after their arrival at a military camp in this area. Davis et al.[8] describe a small group epidemic in the Panoche Valley, immediately west of the San Joaquin Valley. They were able to isolate the fungus from the soil at the actual place where the infection occurred.

Persons of either sex at any age may contract the primary infection. The large number of migratory workers that entered the San Joaquin Valley from the middle west during the past six years have for the most part become infected by *Coccidioides immitis*. This, according to C. E. Smith,[5] resulted in a proportionate increase of "Valley Fever" cases. A similar event is undoubtedly occurring among considerable numbers of military personnel transferred to this area for training. The opportunity for observing early manifestations of primary coccidioidomycosis will, therefore, be greater than usual during this particular period until all new residents of the valley have experienced their infections.

There are no pathognomonic symptoms of the initial coccidioidal infection.[9, 10] They closely simulate those of influenza or bronchopneumonia, or a severe "cold." General malaise with weakness, headache, muscle pains, pleurisy, cough, and gastrointestinal disturbances are common. There is accompanying moderate fever, and chills and night sweats may be present. Sputum accompanying the usual productive cough is small in amount, mucoid or mucopurulent, and frequently blood-streaked. Erythema nodosum or multiforme occurs in 2 to 5 per cent of the cases within eight to 14 days following the onset.

Complete histologic studies of the primary disease in human material are not available. Its exact nature has been suggested by the work of Cronkite and Lack,[11] who were able experimentally to infect 42 per cent of 72 guinea pigs by permitting them to inhale the chlamydospores. The resulting pulmonary infection, appearing eight to 21 days later, consisted of small grayish nodules, up to 5 mm. in diameter, resembling the lesions of miliary tuberculosis. Histologically, they were fairly typical granulomata, involving interstitial spaces and showing little or no alveolar exudate. Mononuclear, epithelioid, and giant cells were present.

Roentgenographic observations of the manifestations of the primary stages of the pulmonary infection are not numerous. This is due, for the

This lesion had cleared completely three months later and patient made uneventful recovery.

D. Patchy consolidation in lower half of right lung in a 35 year old American airplane mechanic. He came to the San Joaquin Valley one month previously from New York state. Sputum positive for *Coccidioides immitis*.

Lesion had completely cleared at the end of two months and patient made an uneventful recovery.

most part, to failure to suspect the existence of primary coccidioidal infection or to confusing it with "influenza," a "cold," or pneumonia. The patient may not even appear for medical care, unless he happens to develop erythema nodosum, which, as stated previously, is present in only one out of 20 cases.

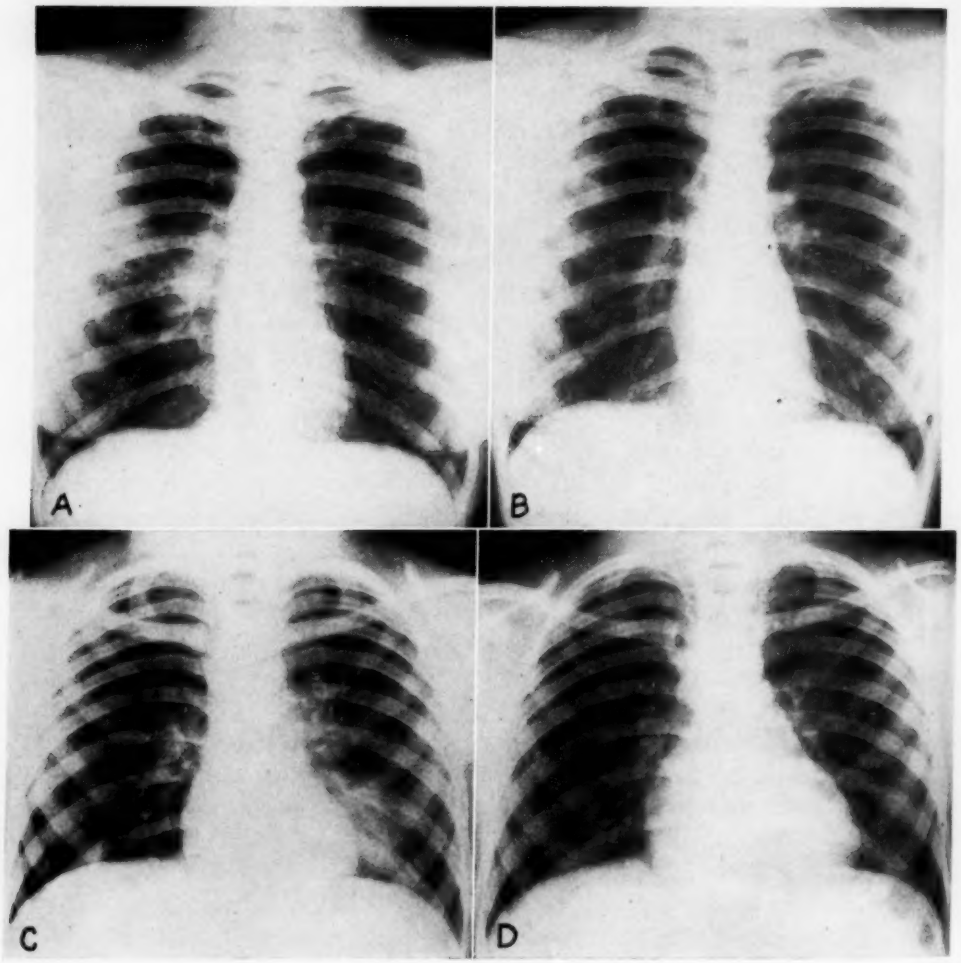

FIG. 2. *A.* Showing exudative infiltration beneath the third right interspace and in the peri-hilar area in a 41 year old American housewife, a resident of the San Joaquin Valley for 7 years.

Sputum positive for *Coccidioides immitis.*

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

B. (Five weeks later.) Showing almost complete clearing of lesion. Erythema nodosum appeared five days after the beginning of the acute illness. Patient now clinically well.

C. Showing exudative reaction in base of left lung in an 8 year old Mexican boy who has resided in the San Joaquin Valley all of his life.

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

Serological tests: Strongly positive precipitins and weakly positive complement fixation.

D. (Five and one half months later.) Showing complete clearing of lesion.

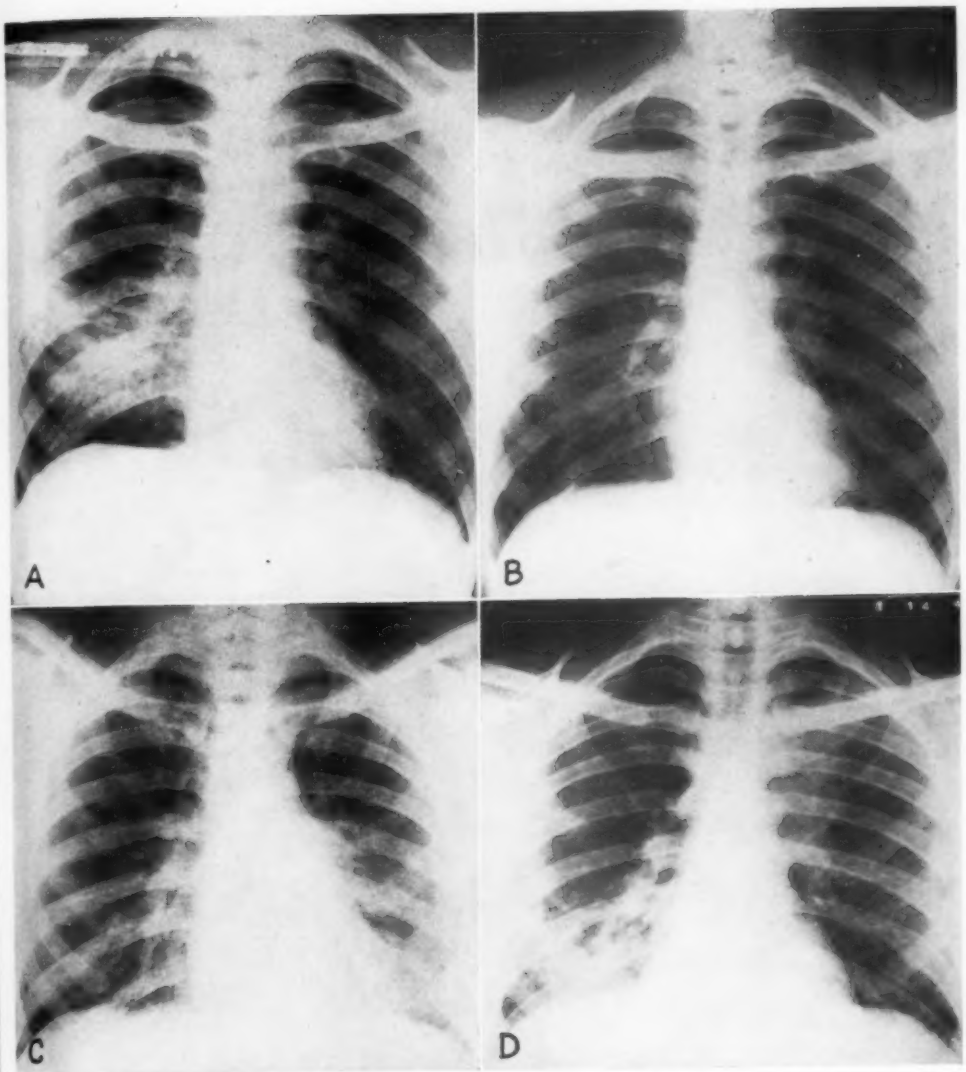

FIG. 3. *A*. Showing involvement of the lower half of the right lung in a 29 year old Negro.

Sputum positive for *Coccidioides immitis*.

Positive cutaneous reaction to 0.1 c.c. of 1 : 1000 coccidioidin.

Resident of San Joaquin Valley for one year.

B. (Five years later.) Showing small amount of residual fibrosis in right base. Patient clinically well.

C. Illustrating exudative infiltration in base of the left lung with early enlargement of lymph nodes in upper left mediastinum appearing five weeks following the onset of an acute chest "cold" in a 27 year old American Negro.

The patient died three months after the onset of present illness and autopsy revealed an abscess of the anterior end of the fourth rib on the left side with extensive pulmonary involvement and marked enlargement of hilus lymph nodes. Miliary abscesses also present in liver, spleen and kidneys. Pus from these loaded with *Coccidioides immitis*.

D. Patchy exudative infiltration in the right base and above the left hilus in a 40 year old Negro who came to the San Joaquin Valley a few months prior to admission.

Sputum positive for *Coccidioides immitis*.

Strongly positive coccidioidin complement fixation and slightly positive precipitins.

Death occurred from meningitis six months following admission.

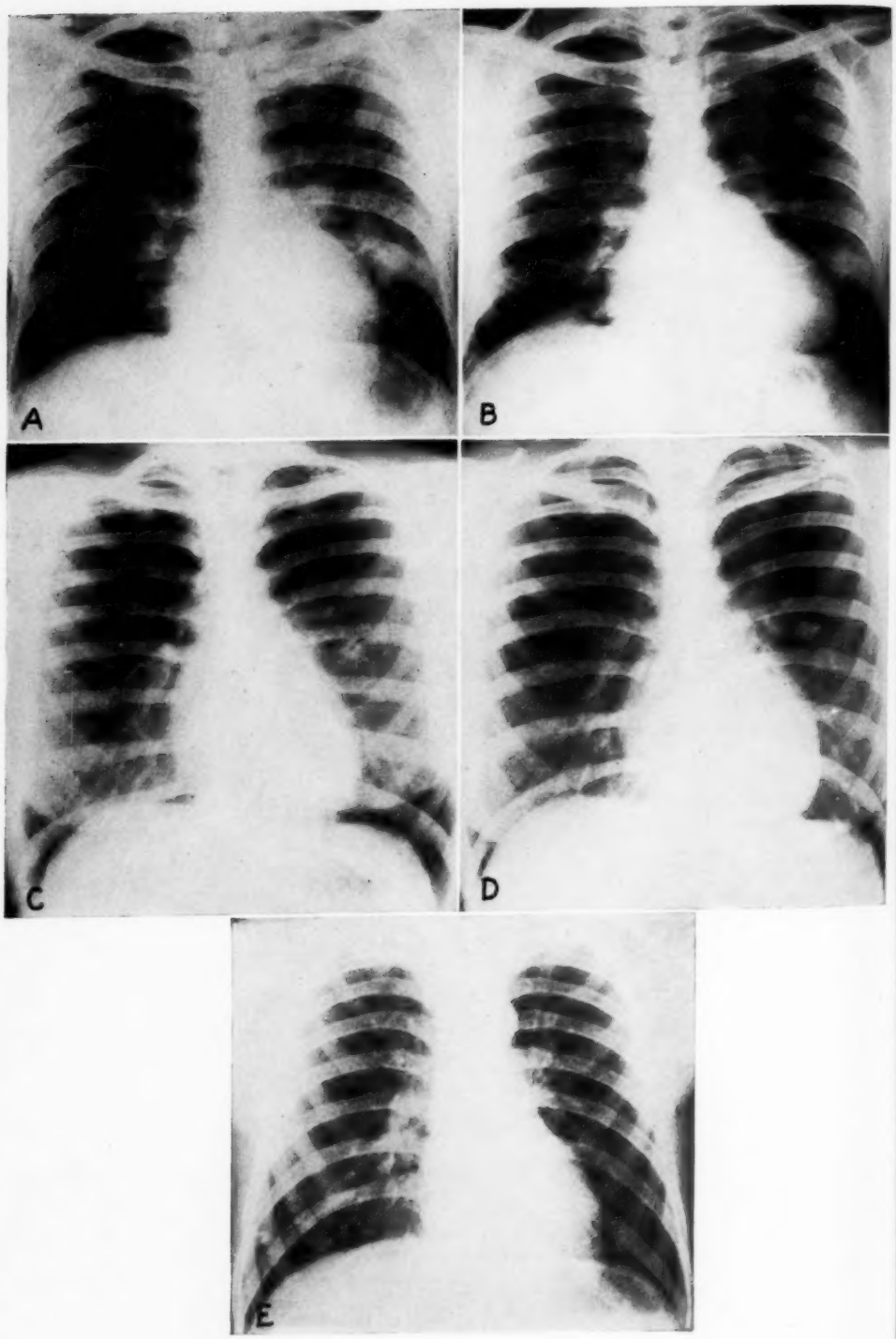

FIG. 4.

Unusual opportunities to observe the early roentgenographic development of the disease have occurred where infection occurred in the laboratory (Dickson [9]), and in an interesting group epidemic among seven college students recently reported by Powers and Starks.[12] In the latter study it was concluded that the early lesions of primary pulmonary coccidioidal infection are usually solitary, though occasionally they may be multiple in number depending upon the degree of infection. The association of cavity formation was also described. Fairly persistent nodules were noted as a part of the pulmonary infiltrate, although the length of observation was not sufficient for possible calcification to occur within these. Each of the seven cases described made a complete clinical recovery. Faber, Smith, and Dickson,[13] reporting on roentgenograms of the chest made in six children soon after the development of erythema nodosum, describe bronchopneumonic-like lesions, suggesting consolidation without lobar distribution. All lesions cleared in a few weeks' time, one forming small deposits of calcium two years later.

Carter [14] has stated that "the detailed roentgen characterization of primary coccidioidomycosis must await repeated observation of many cases, over periods far past the time of clinical illness. This will come from the San Joaquin Valley."

We have observed 40 cases of primary coccidioidomycosis throughout the period of clinical illness and until the roentgenographic pulmonary features have either cleared, remained stable, or progressed. Admittedly, it will be necessary to repeat these observations over many more cases before we can

EXPLANATION OF FIGURE 4.

FIG. 4. *A*. Illustrating scattered nodular productive lesions throughout the left lung field and outside the right hilus in a 29 year old Portuguese who had resided in the San Joaquin Valley for two years.

History of severe chest cold three months previously with persistent productive cough and night sweats.

Sputum positive for *Coccidioides immitis*.

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

Serological tests; positive complement fixation and precipitins.

B. (Approximately one year later.) Showing persistence of residual nodular foci in left lung field and outside of the right hilus. Almost complete clearing of left apex. Patient at work and clinically well.

C. Calcifying fibrotic nodule lying outside and slightly below the left hilus in a 19 year old American girl who has resided in the San Joaquin Valley all her life. Picked up during roentgenogram survey of high school students. No history of acute illness other than "ordinary chest colds."

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

Negative cutaneous reaction to old tuberculin in 1:100 dilution.

D. (Three and one half months later.) Lesion becoming more discrete in appearance and of greater density.

E. This single roentgenogram is representative of a large series showing a calcified parenchymal focus in a person who is clinically well and which probably represents a healed primary coccidioidal infection.

Note calcified lesion lying just above right costo-phrenic angle.

Patient 10 year old boy, born and raised in the San Joaquin Valley, who is in good health.

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

Negative cutaneous reaction to 0.1 c.c. of old tuberculin in 1:100 dilution (repeated) and to PPD second strength.

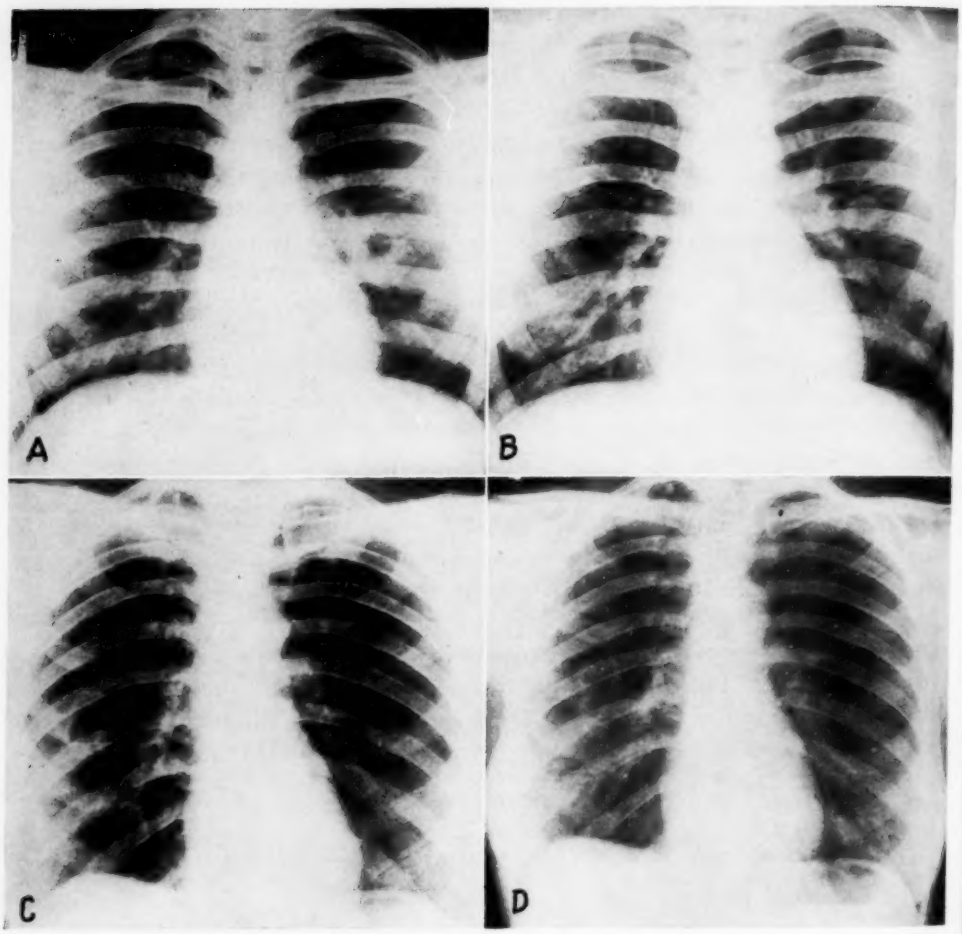

FIG. 5. *A.* Infiltration beneath left hilus showing early development of small cavity in a 22 year old American tractor driver who has lived in the San Joaquin Valley all of his life.

History of "flu" five weeks previously with pain in left side of chest, slight elevation of temperature and occasional productive cough.

Sputum positive for *Coccidioides immitis.*

Positive cutaneous reaction to 0.1 c.c. of 1 : 1000 coccidioidin.

Negative cutaneous reaction to 0.1 c.c. of old tuberculin in 1 : 1000 dilution.

Serological tests: precipitins slightly positive, complement fixation markedly positive.

B. (Three months later.) Considerable clearing and beginning closure of cavity with patient on unrestricted, normal living and working routine. Slight productive cough persists with sputum still positive for *Coccidioides immitis.*

C. Illustrating thin walled cyst-like cavity in the right lung beneath third interspace in a 37 year old American housewife who had lived in the San Joaquin Valley for 15 years.

History of "bronchopneumonia" 11 years previously with three pulmonary hemorrhages and occasional "chest colds" with blood streaked sputum since then.

Gastric contents positive for *Coccidioides immitis.*

Positive cutaneous reaction to 0.1 c.c. of 1 : 1000 coccidioidin.

Negative cutaneous reaction to 0.1 c.c. of old tuberculin 1 : 100 dilution.

Serology: weakly positive complement fixation.

D. (Approximately four years after first roentgenogram.) Showing persistence of cavity. Note calcification in extreme right apex.

finally evolve a clear-cut understanding of the pathogenesis of the infection as revealed by serial roentgenographic observations. Recognizing the fact that the initial infection is for all practical purposes a pulmonary one (Carter [14]), only the primary manifestations as disclosed by roentgenography of the lungs will be considered.

From our series of cases we have selected certain ones as illustrative of important roentgenographic aspects of the primary coccidioidal infection. It was possible in most instances to isolate *Coccidioides immitis* from the sputum. Positive cutaneous reactions to coccidioidin were also present in each case. Serologic studies, in the majority of the patients, revealed the presence of circulating antibodies, and not only confirmed the diagnosis but were suggestive of the particular phase of the infection.*

Depending upon the amount of infection, acute primary coccidioidomycosis varies considerably in the degree of pulmonary involvement. A small nodular area of opacity may be all that is visible (figure 1 *a* and *b*), and on the other hand there may be single (figure 1 *c*) or confluent (figure 1 *d*) areas of pneumonitis, more usual in the pulmonary bases. In many instances the lesions appear to be predominantly exudative in character and clear fairly rapidly (figure 2 *a, b, c, d*). Occasionally, they may leave a small amount of residual fibrosis (figure 3 *a* and *b*). In the Negro and Filipino, perhaps owing to racial susceptibility, we have observed such primary exudative lesions to progress and result in early fatal dissemination of the disease (figure 3 *c* and *d*). There is a tendency for pulmonary foci of primary coccidioidal infection to assume the appearance of productive lesions, and then clear and decrease in size slowly and incompletely, leaving nodular densities that suggest caseation and that eventually may undergo calcification (figure 4 *a* and *b*). Solitary caseo-fibrotic foci undergoing calcification are illustrated in figure 4 *c* and *d*. Figure 4 *e* is illustrative of a large group of healthy children with calcified pulmonary lesions, who have positive cutaneous reactions to coccidioidin (0.1 c.c. of 1 : 1000 dilution) and negative reactions to both old tuberculin (down to and including 0.1 c.c. of 1 : 100 dilution) and to purified protein derivative (second strength). Here, as in primary tuberculous infection, calcification represents a focus of previous coccidioidal infection.

Cavity formation accompanying the early acute phase has been described (Farness and Mills,[15] Powers and Starks,[12] and Winn [16]). Such cavities, usually single, may close spontaneously (figure 5 *a* and *b*). There is, however, a marked tendency for them to persist, despite regression of the other pulmonary lesions (figure 5 *c* and *d*). They then assume a characteristic thin-walled and cyst-like appearance with little or no surrounding collateral

* For most of the bacteriologic confirmation and all of the serologic studies we are indebted to Dr. C. E. Smith and staff of the Department of Public Health, Stanford University School of Medicine. The results of his studies on the serology of coccidioidal infection will be reported in a forthcoming paper. They indicate that precipitins, often marked during the early initial infection, decrease with healing and that complement is fixed only in low dilutions. With dissemination of disease, however, complement fixation apparently rises.

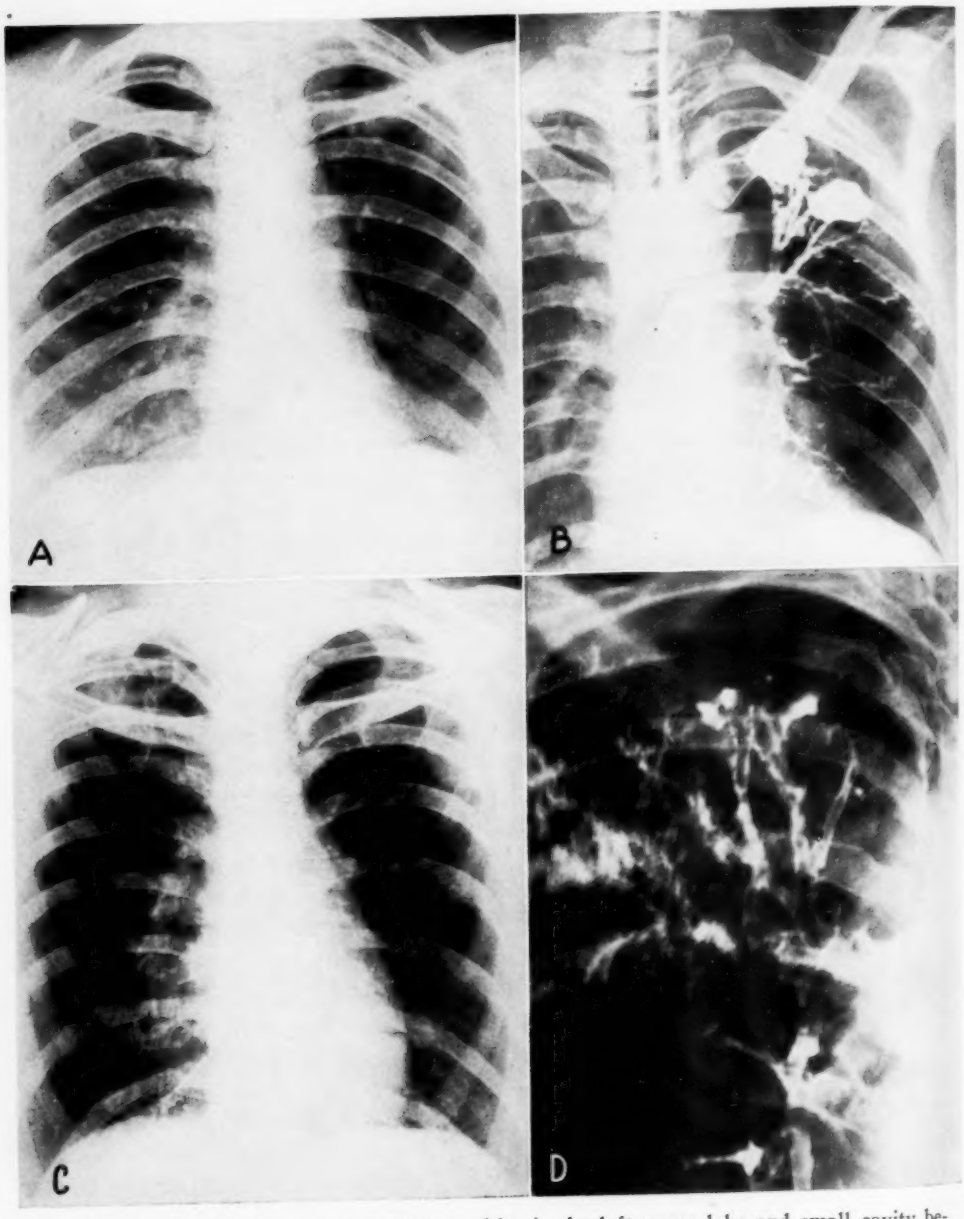

FIG. 6. *A*. Reveals several cyst-like cavities in the left upper lobe and small cavity beneath anterior end of first rib on the right in a 40 year old American housewife who had resided in the San Joaquin Valley for 18 years.

History of hemoptysis six years before, and again two weeks previously with occasional slightly productive cough.

Sputum positive for *Coccidioides immitis*.

Positive cutaneous reaction to 0.1 c.c. of 1 : 1000 coccidioidin.

Serological tests: complement fixation and precipitins markedly positive.

B. Demonstrating the cavitation by injection of iodized poppy seed oil with patient in the horizontal position.

reaction, and change little in size, shape, or appearance over a period of several years. Such cavitation may also be multiple (figure 6 *a* and *b*). Although these cavities serve as reservoirs for the existence and growth of *Coccidioides immitis,* manifested by the continued presence of endosporulating spherules in the sputum, they apparently cause no injury to the health of the person. They are frequently the source of small repeated hemoptyses which may be the only factor leading to their detection.

Localized bronchiectasis may also result from coccidioidal infection, and in one patient an indolent and benign bronchiectatic process was discovered in the right apex, which progressed very slowly over a period of 11 years. Associated clinical manifestations were slight, consisting only of rare blood-streaked and scanty sputum, and the patient remained in good health (figure 6 *c* and *d*).

Initial infection is sometimes manifested by a primary pleuritic effusion, no different from that seen in latent tuberculosis, with the exception that *Coccidioides immitis* may be recovered from the fluid (figure 7 *a* and *b*). As observed by us in one instance, complete absorption of the fluid occurred, with reëxpansion of the underlying lung and no residual evidence of the infection other than slight pleural thickening.

Roentgenographic evidence of secondary mediastinal or hilar adenopathy in association with primary coccidioidal infection is infrequent, although it may occur. Such visible adenopathy has, in our experience, proved a sign of ill omen, preceding fatal dissemination of the disease.

It is unusual for primary coccidioidomycosis to become a progressive disease. When it does so it may assume either an acute or chronic course as it disseminates. Distribution suggests systemic seeding via the blood stream, with entry into the stream occurring from involved lymph nodes. Hence, the serious implication of advancing adenopathy following the initial infection.

Acute disseminating primary coccidioidomycosis is probably always fatal. In our experience the illness may run its course in from five weeks' to seven months' time. The most virulent infection of this type that we have seen occurred in a 36 year old Filipino, and was of miliary type and distribution, associated with multiple verrucous skin lesions over the face, upper trunk, and extremities (figure 7 *c* and *d*). Death occurred five weeks after the onset of the illness, and necropsy disclosed miliary nodules throughout the lungs, spleen, and liver.

C. A 25-year-old American housewife who has complained for the past 11 years of a persistent and slightly productive cough with occasional blood-streaked sputum.

Since the first roentgenogram made 10 years ago there has been slowly progressive fibrosis and bronchiectatic-type change in the right apex, as disclosed by this film.

Sputum now positive for *Coccidioides immitis.*

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

Coccidioidin complement fixation markedly positive.

D. Instillation of iodized poppy seed oil partly outlines sacculated bronchial defects in the right apex, verified by fluoroscopy.

Impression: Localized apical bronchiectasis of coccidioidal type.

FIG. 7.

Prominent mediastinal or hilus adenopathy followed by dissemination is illustrated in figures 8 and 9. Necropsy disclosed extensive disease, sometimes associated with meningitis.

Chronic disseminating coccidioidomycosis (coccidioidal granuloma) has a 50 to 60 per cent mortality. This form, characterized by the frequency of accompanying extrapulmonary lesions and the tendency toward abscess formation, was for 45 years the only recognized form of coccidioidal infection. Its pathology has been well described by Ophuls,[17] and the roentgenographic appearance by Carter.[14, 18, 19]

Summary

The roentgenographic features of the pulmonary pathologic changes produced by primary coccidioidomycosis, both retrogressive and progressive, have been described. Our deductions are based upon the close observation of 40 cases of primary coccidioidal infection, in which the course of the infection has been outlined by serial roentgenographic and clinical follow-up studies.

The different types of exudative and productive pulmonary lesions have been described, as well as the tendency of the primary form of the disease to heal. Attention has also been called to certain pulmonary changes residual to primary coccidioidomycosis, including calcification and cyst-like cavities, the latter frequently associated with hemoptysis. Uncommonly, primary coccidioidal infection may become progressive, assuming either an acute or chronic (coccidioidal granuloma) form of dissemination, with an associated high mortality.

FIG. 7.

Explanation of Figure 7

FIG. 7. *A.* Hydropneumothorax and atelectatic lung in a 17 year old boy who had resided in the San Joaquin Valley for four years.

Culture of the slightly turbid fluid removed from the chest revealed an abundant growth of *Coccidioides immitis,* confirmed by animal inoculation.

Positive cutaneous reaction to 0.1 c.c. of 1:1000 coccidioidin.

Negative cutaneous reaction to 0.1 c.c. of 1:100 old tuberculin.

B. (Fifteen months later.) Lung expanded and no evidence of definite parenchymal lesion.

Serological tests: markedly positive complement fixation at first, later becoming weaker with clinical improvement.

C. Illustrating consolidated area in base of left lung and finely stippled infiltration throughout the remainder of both lung fields of miliary type. Note pleural calcification on right side. This occurred in a 36 year old Filipino vineyard worker, who had resided in the San Joaquin Valley for six years. There were extensive multiple verrucous skin lesions on the face, back and extremities.

Death occurred five weeks after onset of present illness. Autopsy disclosed disseminated disease of miliary type without gross lymphadenopathy.

Sputum and serum from skin lesions contained spherules of *Coccidioides immitis.*

Serological tests: strongly positive complement fixation and precipitins indicating acutely disseminating primary infection.

Patient gave negative reactions to coccidioidin and old tuberculin down to 1:10 dilution, (anergic).

D. Showing appearance and distribution of verrucous skin lesions.

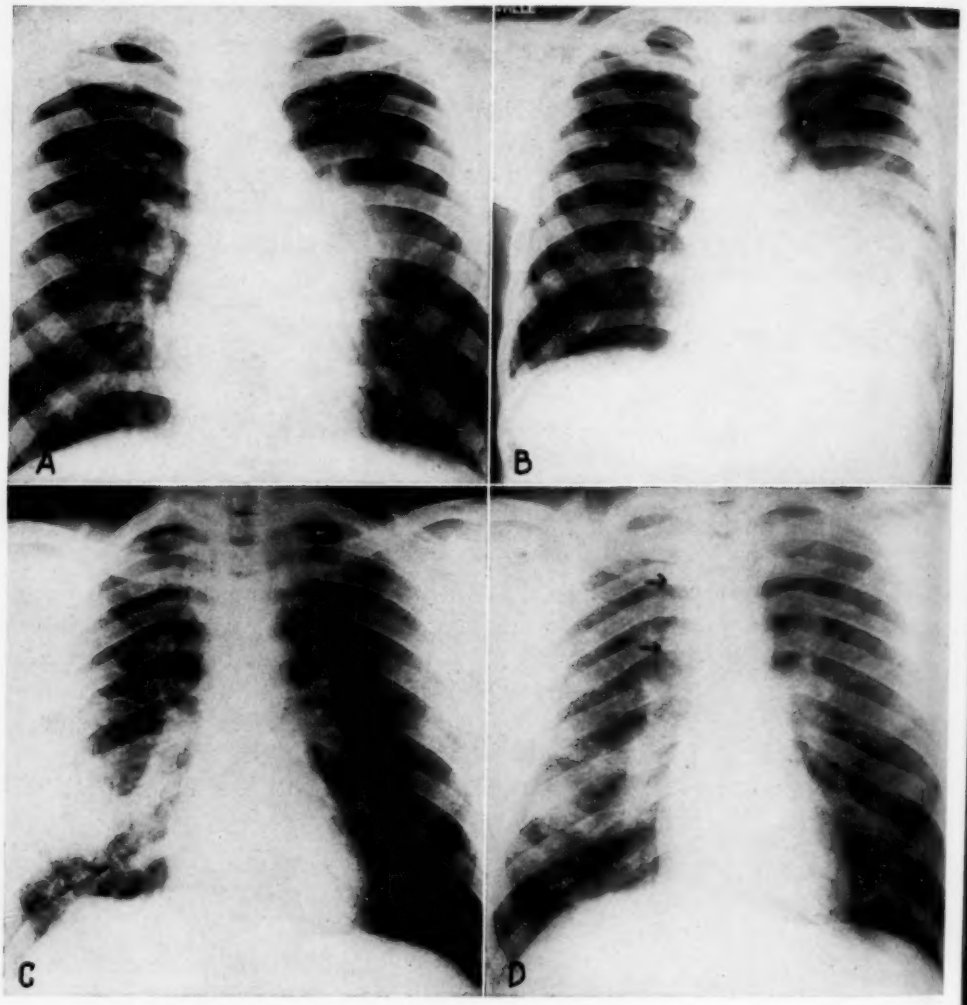

FIG. 8. *A.* Marked left hilus lymphadenopathy with some peri-hilar haziness and peribronchial infiltration in the left base in a 13 year old American school boy who had resided in the San Joaquin Valley for two years. There were associated erythema multiforme-like lesions of unusually chronic type.

Sputum positive for *Coccidioides immitis.*

B. (One month later.) Artificial pneumothorax on the left discloses the mediastinal and hilus lymphadenopathy. Small pleural effusion positive for *Coccidioides immitis.*

Death seven months from onset of present illness with extensive disseminated miliary disease, and enlarged caseous mediastinal lymph nodes at autopsy.

C. Showing a dense rounded area of consolidation in the base of the right lung with some peribronchial infiltration in a 26 year old American bus driver who had resided in the San Joaquin Valley for 1½ years.

Sputum positive for *Coccidioides immitis.*

D. (Two months later.) Marked clearing of the density in the right base, but the appearance of lymphadenopathy above the right hilus. This was followed by death in two months from disseminated disease, including meningitis.

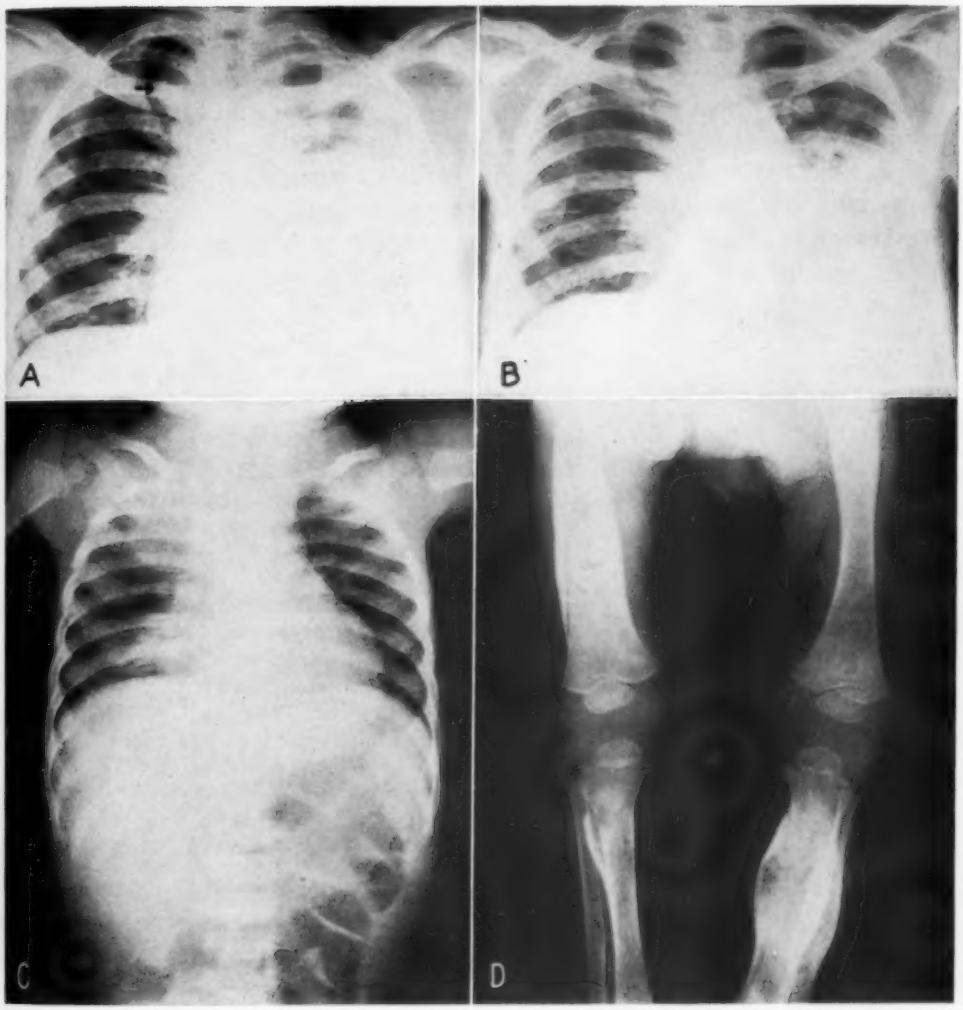

FIG. 9. *A*. Illustrating left pleural effusion and mediastinal lymphadenopathy in a 41 year old Filipino farm laborer who had lived in the San Joaquin Valley five years. History of four months' chronic cough and weakness.

Sputum positive for *Coccidioides immitis*. Chest fluid negative.

Note greatly enlarged mediastinal lymph node projecting outward from right border of upper mediastinum.

B. (Eleven days later.) Showing bronchogenic spread on the right and consolidation of the left lung in the lower half.

Death occurred in six weeks from disseminated disease.

Impression: Acute disseminated primary coccidioidomycosis.

C. Illustrating areas of consolidation in the right upper lobe and base of the right lung in a five months old Negro infant. Note widening of upper mediastinum indicating adenopathy.

Coccidioides immitis present in gastric contents and in pus from bone lesions.

Impression: Acute primary progressive coccidioidomycosis.

D. (Illustrating bone lesion.) Showing multiple destructive bone lesions in the tibia, femur, fibula, ulna, skull and left metacarpal.

Death in four months; autopsy disclosed abscesses in liver and spleen, and marked caseous mediastinal lymphadenopathy.

Recognition of primary coccidioidomycosis depends upon keeping the possibility of the disease in mind, especially if the patient gives a history of residency within an endemic area. Cases of suspected pulmonary tuberculosis, with persistently negative sputum, represent possible coccidioidal infection.

The coming of large numbers of uninfected persons, especially military personnel, into the inland California valleys and certain parts of Arizona and Texas, will result in a proportionate increase of the incidence of coccidioidal infection.

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VITAMIN B THERAPY IN PARALYSIS AGITANS*

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THE numerous therapeutic approaches to the problem of paralysis agitans indicate clearly the inherent difficulties in this problem. It is, therefore, only natural that several investigators have recently turned to vitamin therapy in the hope of finding a more effective weapon for attacking this apparently incurable disease.

It is noteworthy that of the six cases reported by Parkinson in his original essay on the shaking palsy one patient attributed his symptoms to over-indulgence in alcohol and another to a long period of neglect in a Spanish prison.[1] Furthermore, Kikuchi states that monkeys with experimental B-avitaminosis develop mask-like facies, propulsory movements with forward stooping, occasional tremors and increased lacrimation with salivation.[2] Finally, it was noted that among 50 pellagrins attending the nutrition clinic at Birmingham, 10 had extrapyramidal signs and five of these showed "mild Parkinsonism" without any antecedent history of encephalitis.[3]

Jolliffe administered pyridoxine in doses of 50 to 100 mg. intravenously, either daily or every other day, to 15 patients with paralysis agitans. Four showed subjective and definite objective improvement. Two additional patients were subjectively improved. Of the 11 patients who showed no objective improvement, 10 had suffered disability for more than three years, and five of these gave a history of encephalitis.[4, 5]

Spies soon confirmed this observation and reported "dramatic improvement," particularly of the tremor, in patients having postencephalitic Parkinson's disease. In the arteriosclerotic group their results were not nearly so good.[6]

Jolliffe subsequently reported a group of 32 ambulatory patients with Parkinson's disease. In this latter group he noted that improvement seemed best in the postencephalitic group. In that group six of the 10 patients showed subjective improvement, all of whom were continuing treatment. Of these, however, only four showed objective improvement, and two had returned to work. In the idiopathic group six of the 16 patients showed subjective improvement, but only two objective improvement. He conservatively concludes that the syndrome of paralysis agitans seems to include people who are helped by pyridoxine.[7]

In a personal communication, it was learned that five of the 25 patients in Spies' clinic were showing improvement on pyridoxine therapy, but Bean [8]

* Received for publication August 8, 1941.

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notes that some of his co-workers were not obtaining favorable results with other non-clinic patients.

It was decided, therefore, to observe the effects of vitamin B therapy on a group of patients with paralysis agitans.

Method. Twenty-two unselected patients were used as subjects. Of these four were idiopathic, 14 were postencephalitic, three were arteriosclerotic, and one was post-traumatic. Their ages ranged from 28 years to 72 years, the average being 49.2 years. The duration of symptoms varied from three years to 33 years, the average being 14.4 years. It should, therefore, be particularly noted that we were dealing almost entirely with *very chronic* cases.

The patients were then divided into two groups, comparable in type, age, and duration of symptoms. One group of 12 patients was on the neurological service. They received daily intravenous doses of the vitamin preparation. The other group, comprising 10 patients, was not on the neurological service, and prior to the onset of the present study was composed of more or less ignored custodial cases. They received daily injections of 5 c.c. of normal saline.*

The vitamin preparations will be referred to as A and B.†

Preparation A	Contents	Preparation B
10 mg.	Thiamin chloride	10 mg.
10 mg.	Nicotinic acid amide	10 mg.
1 mg.	Riboflavin	1 mg.
10 mg.	Pyridoxine hydrochloride	100 mg.
5 c.c.	Buffered solvent q.s. ad.	5 c.c.

All patients were continued on whatever other therapy they were receiving prior to the onset of the experiment, so that any effects noted could be related to the added therapy. Each case was carefully reëxamined at the start of the experiment, and then again at weekly intervals until the experiment was completed. The following points were then recorded on a special chart: Facies, condition of skin and hair, body attitude, gait, rigidity, strength (hand dynamometer measurements), speech, handwriting (timed), sleep habits, emotional status, and patient's evaluation of treatment.

Each group received six intravenous injections a week. The vitamin treated group received preparation A for five and a half weeks and preparation B for five weeks. The control group received daily injections of 5 c.c. of sterile saline for ten and a half weeks. Overenthusiasm was avoided. The patients were all told that they were receiving vitamin treatment, and that we hoped it would help them.

* Prior to the onset of the present experiment, both groups had received the usual treatments for paralysis agitans. These included drugs of the atropine series, fever therapy, quinine, benzedrine, intramuscular B complex, thiamin and nicotinic acid intramuscularly, Rabellon and bellabulgara. None of these therapeutic procedures had altered the course of the disease, but in some cases troublesome symptoms had been partially relieved.

† Kindly supplied in sterile, single-dose "poly-B" ampoules through the courtesy of Dr. H. E. Dubin, Technical Director of the U. S. Vitamin Corporation, New York.

Results

1. In both normal and control groups, it was noted that the symptomatology varied considerably from examination to examination, frequently from day to day, or even during the course of the same day.

2. No objective changes were noted in the vitamin treated group. Two of these patients claimed subjective improvement, but showed no objective change. One, chair-fast for the previous year, disliked her injections so much that she sought to avoid them by walking to the bathroom each morning. Otherwise, she showed no objective change for the better. None of the patients in this group was enthusiastic about the treatment. One patient developed intestinal obstruction (volvulus) during the course of the treatment, necessitating operation. He eventually died of postoperative pneumonia.

3. Nine of the control group were very enthusiastic about the effects of the treatment for the first two weeks, but thereafter only three persisted in their subjective improvement. One of these patients, who had been incontinent and bedfast, began to get up daily and walk to the bathroom, a distance of 75 yards. He showed no other objective improvement. Interestingly, he had performed similarly while receiving whole belladonna root therapy for the first time the preceding year.

4. Three partially bald males receiving the vitamin preparations showed a regrowth of fine lanugo hair over the vertex. One female, whose hair had been falling out, said that this ceased after two weeks of therapy. Spies noted similar results with nicotinamide.[9]

5. Beneficial results in insomnia have been noted with vitamin B_6.[9] This was not apparent in our cases, and insomnia continued to be a troublesome symptom to about two-thirds of our patients.

Discussion

In evaluating the results of vitamin therapy in a group of patients suffering from any chronic illness, the following factors must be kept in mind:

A. The Specific Vitamin Action of the Material Used. There is no evidence indicating that paralysis agitans is causally related to any specific vitamin deficiency. There is at the present time a particularly great need for more expert laboratory technics. Of course, we do not suggest that clinical experimentation should stop until these aids are available, but we do believe that clinical experimentation in this field will be much better directed, and the therapeutic results much easier to evaluate when these methods become available.

B. The Non-Specific Actions of Vitamins. Vitamins are not only accessory foodstuffs, but also drugs. Thus, nicotinic acid is not only a vitamin, but also a vasodilator drug. Its vitamin and enzyme effects need bear no relationship to its use as a vasodilator drug. In addition, thiamin, nicotinic acid and pyridoxine are pyridine derivatives, and riboflavin is easily

convertible into a pyridine. As such, the action of these substances may be on a purely pharmacological basis and need bear no relationship to their vitamin and enzyme properties.

C. Psychological Factors. It must be remembered that individuals attempt to maintain the experience of health even when threatened by a serious illness. The metabolic approach to these "degenerative" diseases has filled both patient and physician with a much needed optimism. In our patients the psychological effects of treatment were clearly demonstrable in our control group. These custodial cases, hitherto almost ignored, in general showed a better response to therapy than did our vitamin treated cases.

D. Stage at Which Treatment Is Instituted. Vitamin therapy to be efficacious must be instituted early. This is clearly demonstrated by the difference in the results from those previously reported by Jolliffe and Spies, who were in general treating cases of much more recent origin. Pathological processes are affected by therapy only when treatment is instituted before irreversible structural changes have occurred. This fact is worth the utmost consideration in evaluating therapeutic results and undoubtedly accounts for many differences in reported observations.

Conclusions

1. Twelve cases of long-standing paralysis agitans were treated with large amounts of the "B" vitamins and two showed subjective improvement. In no instance was there any objective change for the better.

2. Ten cases of long-standing paralysis agitans were treated with saline. Nine showed initial subjective improvement, and this persisted throughout the treatment in three instances. One of these latter showed objective improvement.

3. In the vitamin treated cases, three partially bald males showed some regrowth of hair. One female stated that her hair had ceased falling out.

4. Some of the difficulties in evaluating vitamin therapy in these cases are discussed.

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THE URINARY TRACT IN DIABETIC WOMEN; ITS CONTRIBUTION TO THE INCIDENCE OF HYPERTENSION *

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It has appeared to us that infection of the urinary tract has been a relatively frequent finding in diabetic patients, especially in women. Perhaps it is because numerous observations such as are cited in the following statements have brought this forcibly to our attention. An obese woman, who from past experiences should require little or no insulin to control the diabetes, is found to tolerate large doses. A search for a cause for this insulin resistance has often revealed a hidden infection in the urinary tract, treatment of which permitted a reduction of the insulin dosage. Further, when a diabetic patient, particularly a woman, is admitted to the hospital with fever, if the cause is not readily determined, the study of the catheterized specimen of urine often reveals it.

In diabetic women three unavoidable difficulties interfere with the diagnosis of infection of the urinary tract by routine clinical procedures. First, it is often impossible to differentiate between symptoms, either past or present, referable to diabetes and those caused by a possible urinary tract infection; secondly, even more important is the repeated observation that severe infection may be present without symptoms; and thirdly, it is well known that the interpretation of pus and bacteria in voided urine from the human female is commonly impossible, so that one can easily and conscientiously ignore even a report of "numerous white blood cells," especially if no symptoms are present. We, as those in other clinics, have hesitated to employ routine catheterization of the bladder and consequently have done this only when there appeared to be adequate reasons.

The following experience supports the concept that diabetic women are particularly vulnerable to infections of the urinary tract. During the past 15 months four diabetic women, who previously had not been under our care, were admitted to the Buffalo General Hospital with a history of chills and fever of short duration; all of them were profoundly ill, mentally confused and stuporous. Acidosis was not present. The *Bacillus coli* was cultured from the blood stream of three of the patients, and the *Bacillus*

* Received for publication March 15, 1940.

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Acknowledgments: To Dr. Frederick J. Parmenter, Chief of the Urologic Service, for his fine coöperation and assistance. To Dr. Ernest Witebsky, for the bacteriological studies and for his criticisms. To Dr. Edward C. Koenig, for the interpretation of the pyelograms. To Dr. James G. Fowler, for the retinoscopic examinations and their interpretations; and to Dr. Thomas F. Barrett and Dr. Frank C. Hoak, associates in the diabetic clinic, for their assistance in the gathering of data.

aerogenes capsulatus from the fourth. All of the patients had an obvious infection of the urinary tract, and the identical organism was found in the catheterized urine as was cultured from the blood. (These patients are not included with those in this report but will be the basis of a subsequent publication.)

Probably more important is the consideration of the influence of chronic infection of the upper urinary tract (chronic pyelonephritis) on arterial hypertension, a finding which is so frequently encountered in older diabetic patients, especially women. This was, of course, suggested to us by the recent contributions on that subject which have appeared in the literature.

Plan of Study

The Patients Studied. Only women were observed, all between the age 36 to 79 years, three being under 40. The majority of the patients had been under our observation in a diabetic clinic for a considerable period. They were admitted to the wards for study, several each week, as they visited the clinic. Also, patients who were in the hospital for other reasons were included in the study. The diabetes was controlled at the time of the examinations. The study was done without consideration of suspected involvement of the urinary tract. Patients whose state was such that it seemed imprudent to subject them to the examination were rejected as subjects.

The Urologic Examination. Before the cystoscope was passed the patients were asked to empty their bladder as completely as possible while in the sitting position. Then the presence or absence of residual urine was determined. If a stricture of the urethra was found, dilatation was carried out before cystoscopy. Specimens of urine were obtained from the bladder and kidneys for immediate microscopic examination; then, if cultures could not be made at once, they were placed in the ice box in the bacteriological laboratory. Renal function was determined by the injection of 1 c.c. of a standard phenolsulphonphthalein solution intravenously; urine specimens were collected from the kidneys and bladder at the end of one-half hour. The percentage of the dye in the transvesical leakage, when this occurred, was divided and added equally to the percentages of the dye coming from the kidneys. All patients but one had a retrograde pyelographic study. In this one case an intravenous pyelogram was obtained. The out-patients remained in the hospital for 24 to 48 hours unless a post-cystoscopic reaction occurred which it did in a few instances but was never severe or serious.

The data obtained in 84 cases studied in the above manner have been placed in six tables each representing a group of cases. The patients were grouped in accordance with the involvement of the upper or lower urinary tract and those who showed abnormalities of the upper urinary tract were again subdivided with respect to the renal function as determined by the 'phthalein test. These divisions are explained in the headings of the tables.

KEY TO TABLES I, II, III, IV, V, VI

Retinal Arteriosclerosis. The grades were defined as follows: Grade 1, slight pressure of the arteries on the veins, uneven calibre and an increase in the light reflex stripe; grade 2, an increase in these changes; grade 3, evidence of advanced arteriosclerosis together with hemorrhages or exudates or both.

Stricture of Urethra. Stricture was considered absent when a cystoscope, No. 24 F, could be passed freely. Grade 1 stricture was held to be present when this instrument was passed with difficulty; grade 2, when it was necessary to start dilatation by a bougie of moderate size; grade 3, when it was necessary to start dilatation with a small bougie.

Cystocele. Grades 1, 2 and 3 (no qualification necessary).

Bladder. "In." (signifies *intensity* of inflammation of the bladder): Grade 1, a trigonitis —an accentuation of the normal vascular distribution; a fusion of the capillaries and a loss of their individual characteristics; grade 2, when the inflammatory process was extended to involve the base of the bladder; grade 3, involvement of the entire bladder with redness, a loss of normal vascular markings, often with bullous edema and trabeculation. "P." (pus in the urine): Grade 1, scattered leukocytes; grade 2, a visible sediment of leukocytes in the centrifuge tube; grade 3, marked pyuria. "B." (bacteria in the stained smear): Grades 1, 2 and 3 (no qualification necessary).

Ureters and Kidneys. "St." (stone in ureter). "Na." (narrowing of ureter): Grade 1, slight; grade 2, moderate; grade 3, extreme. "Bl." (blunting of calyces): Grade 1, slight; grade 2, moderate; grade 3, extreme. "B." (bacteria in stained smear, as under "Bladder"). "P." (pus in urine, as under "Bladder").

Table I: *Patients with Bilateral Reduction of Kidney Function* (group I). There were six patients in this group, five of whom had well established hypertension. Cases 1, 2 and 3 had evidence of pyelonephritis with active infection on one or both sides at the time of the examination. Infection in the upper urinary tract was either absent or minimal in cases 4, 5, and 6, but since blunting of the calyces and hydronephrosis were present in some degree on one or both sides it is possible that they had had pyelonephritis which had subsided. A grade 2 or 3 retinal arteriosclerosis was present in four of the patients; the remaining two had cataracts.

Table II: *Patients with Unilateral Reduction of Function with Bilateral Urologic Lesions* (group II). There were 16 patients in this group, 13 of whom had hypertension. Twelve had bilateral infection and in addition one, case 10, had complete obstruction of one ureter and infection on the other side. Also, case 11 had or had had an infection on the left side where the 'phthalein excretion in one-half hour was but 3 per cent. Similarly, case 13 probably had bilateral infection although the urine from the left side was not cultured, but there was evidence of extreme damage to the kidney pelvis and ureter and no 'phthalein was excreted. Only case 15 in this group was completely free of evidence of infection in the upper urinary tract. A retinoscopic examination was not carried out on one of the 16 patients; of the remaining, five had grade 2 and one had grade 3 arteriosclerotic retinitis. Three had cataracts and one had glaucoma. Four had normal fundi.

Table III: *Patients with Bilateral Normal Kidney Function and Bilateral Urologic Lesions* (group III). Fifteen patients comprised this group. Eight of these had hypertension, although none had an extreme grade. Nine had active infection on one or both sides. In the remaining six cases there were various grades and combinations of hydronephrosis, hydroureter, and blunting of the calyces bilaterally. Evidence of arteriosclerosis of the retinal

TABLE I

Patients with Bilateral Reduction of Kidney Function

Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Lower Urinary Tract					Upper Urinary Tract					
			Sys.	Dias.		Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Bladder	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
1	48	3	185	100	Cataracts	0	0	0	In.-1; B.-1	*B. coli*	Na.-1; Hy.-2; St.; B.-2	11	*B. coli*	Hy.-1; B.-0	2	0
2	58	0	204	94	3	0	0	30	P.-3; B.-3; In.-3	*B. coli* *Staph. aur.*	P.-1; B.-3	6	*B. coli*	P.-3; B.-3	6	*B. coli*
3	62	0	210	130	2	0	0	0	P.-1	Enterococcus; *B. aerogenes cap.*	Hy.-3; Bl.-1; Ptosis P.-1; B.-2	6	Enterococcus; *B. aerogenes cap.*	0	7.6	Enterococcus; *B. aerogenes cap.*
4	46	8	186	130	3	0	3	210	In.-1; P.-1	0	Hy.-1; Bl.-1	14	0	Hy.-1; Bl.-1	17	Anerobic strept.
5	56	2	190	95	2	3	1	120	In.-1; P.-1	*B. coli;* anerobic gram negative bac.	P.-1; Bl.-1; Ptosis	15	0	0	11	Anerobic gram negative bac.
6	53	1	130	90	Left cataract	0	0	240 (?)	In.-1;	0	Bl.-1	15	0	Hy.-2; Bl.-3	16	0

TABLE II

Patients with Unilateral Reduction of Kidney Function and Bilateral Urologic Lesions

						Lower Urinary Tract					Upper Urinary Tract					
Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Cystitis	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
			Sys.	Dias.												
1	72	3	240	100	Early cataracts	1	1	0	In.-0; P.-1; B.-3	*B. coli*	P.-1; B.-0	24	*B. coli*	P.-2; B.-3	7	*B. coli*
2	67	1	190	90	1	0	1	180	P.-1; B.-1	*B. aerogenes cap.*	Hy.-3; P.-1; B.-1	35	*B. aerogenes cap.*	Hy.-3; P.-1; B.-1	16	*B. aerogenes cap.*
3	43	2	198	100	Glaucoma	3	3	0	In.-1; P.-1; B.-1	*B. coli;* enterococcus	Hy.-2; P.-1; B.-1	15	*B. coli;* enterococcus	P.-1; B.-1	25	*B. coli;* enterococcus
4	72	—	150	80	0	0	1	90	In.-1; P.-1; B.-1	*B. coli;* enterococcus	Hy.-2; P.-1; B.-1	15	*B. coli;* enterococcus	P.-1; B.-1	25	*B. coli;* enterococcus
5	59	11	155	90	Early cataracts	0	2	0	In.-3; P.-1; B.-2	*B. coli*	Hy.-3; Bl.-2; P.-1; B.-1	22	*B. coli*	Bl.-1; Hy.-2; P.-1; B.-1	15	*B. coli*
6	57	8	180	100	1	0	0	0	P.-1; B.-1	*Pseudomonas aeruginosa*	P.-1; B.-1	24	*Pseudomonas aeruginosa*	P.-1; B.-1	7	*Pseudomonas aeruginosa*
7	57	0	160	90	Cataracts	0	1	60	In.-1; P.-1; B.-1	*B. coli*	P.-1; B.-1; Bl.-1; Hy. ureter	16	*B. coli*	Bl.-2; Hy. ureter	33	*B. coli*
8	52	5	160	90	0	0	0	180	In.-3; P.-1; B.-3	*B. coli*	P.-1; Hy.-1; Bl.-1	8	*B. coli*	0	25	*B. coli*

TABLE II—*Continued*

Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Lower Urinary Tract					Upper Urinary Tract					
			Sys.	Dias.		Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Cystitis	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
9	52	2	165	90	0	0	1	180	In.-1; P.-1	*Staph. aur. hem.*	Hy.-1; Hy. ureter	29	*Staph. aur. hem.*	Bl.-1	18	*Staph. aur. hem.*
10	64	8	200	120	3	1	1	180	In.-3; P.-3; B.-3	*B. coli;* entero-coccus	Ptosis; complete obstruction	—	—	P.-1; dilated ureter	25	*B. coli;* entero-coccus
11	59	5	190	100	1	3	1	0	In.-1; P.-2; B.-3	*B. proteus*	Hy.-2; P.-1; B.-2; Bl.-3; Hy. ureter	37	*B. proteus*	P.-1; B.-1	3	—
12	65	8	200	104	0	3	1	0	In.-3; B.-3	*B. coli; Strept. hem.*	P.-1; B.-1; Hy.-2	21	*B. coli*	St.; B.-1; Hy.-2	3	*B. coli*
13	64	8	150	100	0	0	3	0	In.-1	*Strept. hem.*	Hy.-1; Bl.-3; Hy. ureter	26	*Strept. hem.*	Hy.-1; Bl.-3; Hy. ureter	0	—
14	36	1	160	100	2	2	1	0	In.-1; P.-3; B.-3	*B. coli*	P.-3; Hy.-2; B.-3; Bl.-2; Na.-1	13	*B. coli*	P.-3; B.-3	50	*B. coli*
15	51	3	208	102	1	0	0	0	In.-1; P.-1	0	0	10	0	0	26	0
16	60	6	132	84	1	3	1	75	In.-3; P.-3; B.-1	Entero-coccus	P.-1; Hy.-2; Ptosis	23	Entero-coccus	0	7	Entero-coccus

TABLE III

Patients with Bilateral Normal Kidney Function and Bilateral Urologic Lesions

						Lower Urinary Tract					Upper Urinary Tract					
Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Bladder	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
			Sys.	Dias.												
1	52	4	130	80	0	0	1	70	P.-1; B.-1	Anerobic strept.	Hy. ureter P.-1	28	Anerobic strept.	P.-1	26	Anerobic strept.
2	61	1	155 160	80 90	Haziness of lenses	0	1	0	In.-2; P.-1	0	Hy.-1	22	0	Hy.-2	35	0
3	46	3	165	95	3	0	2	60	In.-1; P.-1; B.-1	*B. coli*	St.; Hy.-1; Bl.-2	26	0	P.-1	27	*B. coli*
4	49	6	130	80	Cataracts	3	1	60	In.-1; P.-1; B.-1	Enterococcus; gram neg. gas producing bac.	Hy.-2	29	Enterococcus; gram neg. gas producing bac.	P.-1	20	Enterococcus; gram neg. gas producing bac.
5	62	0	105	80	0	2	1	0	0	Gram pos. cocci	Bl.-1	25	0	Bl.-1	22	0
6	48	6	150	80	1	2	3	0	In.-1; P.-1	0	Hy.-1; ptosis; Bl.-1	19	0	Hy.-1; Bl.-1	27	Hem. strept.
7	69	0	134	78	0	1 (carbuncle)	0	120	In.-3; P.-2; B.-3	*B. alkalescens;* enterococcus	P.-1; B.-1; Hy.-1; Bl.-1; ptosis; hy. ureter	20	*B. alkalescens*	P.-1; B.-1; Hy.-1; Bl.-1; ptosis; hy. ureter	19	*B. alkalescens*

TABLE III—*Continued*

						Lower Urinary Tract					Upper Urinary Tract					
Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Bladder	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
			Sys.	Dias.												
8	59	5	180	80	0	0	1	300	In.-1; (atonic bladder)	0	Hy.-1; Bl.-1; Hy. ureter	34	0	Hy.-1; Bl.-1; Hy. ureter	29	0
9	53	4	170	90	0	0	1	0	In.-3; P.-3; B.-1 (atonic bladder)	*B. coli*	Bl.-1	33	0	Hy.-1; Bl.-1; Hy. ureter; B.-1; P.-1	28	*B. coli*
10	66	7	190	90	1	0	2	150	In.-1; P.-1	*B. coli;* entero-coccus	Hy.-1; Bl.-2	23	0	Hy.-1; Bl.-1	19	Anerobic strept.
11	48	18	140	95	0	0	3	0	In.-3; P.-3; B.-3	*B. coli*	Bl.-2; Hy. ureter; B.-1	19	*B. coli*	Bl.-2; Hy. ureter; B.-1	26	*B. coli*
12	61	2	134	70	0	0	0	15	In.-3; P.-2; B.-2	Entero-coccus; *Staph. aur. hem.*	P.-1	20	Entero-coccus	P.-1	25	Entero-coccus
13	45	3	150	100	0	0	1	0	In.-2; P.-1; B.-2	*B. coli; Staph. aur. hem.*	B.-2	28	*Staph. aur. hem.*	0	25	*Staph. aur. hem.*
14	55	1	180	90	1	0	2	0	In.-1; P.-1	0	Hy.-2; Bl.-2	28	0	Hy.-1	23	0
15	56	2	170	90	2	0	2	180	In.-2; P.-3; B.-2	*B. coli; Proteus morgani*	P.-1; B.-1; Hy.-3; Hy. ureter	31	*B. coli; Proteus morgani*	P.-1; Hy.-1	31	*Proteus morgani*

TABLE IV

Patients with Bilateral Normal Kidney Function and Unilateral Urologic Lesions

						Lower Urinary Tract					Upper Urinary Tract					
Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Bladder	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
			Sys.	Dias.												
1	46	4	130	85	1	0	1	30	0	0	Hy.-1; Bl.-1	20	0	0	23	0
2	61	4	185	90	Cataracts	3	3	80	In.-1; P.-1; B.-3	*B. coli*	P.-1; Bl.-1	23	*B. coli*	0	29	0
3	79	3	200	100	2	2	3	120	In.-1	0	Bl.-1; ptosis	30	Anerobic gram neg. bac.	0	28	0
4	58	3	160	90	1	0	0	0	In.-1; P.-1	Anerobic strept.	Bl.-2	26	0	0	28	0
5	74	7	160	80	1	0	3	0	In.-1	Anerobic strept.	—	32	0	Bl.-1; P.-1	27	Anerobic strept.
6	66	11	160	85	Cataracts	2	3	0	P.-1; B.-1	*Staph. aur. hem.*	St.; Hy.-1	28	0	0	27	0
7	48	16	130	82	0	0	1	0	In.-1; P.-1	0	P.-1; B.-1	36	*B. coli*	0	35	0
8	43	5	150	95	0	0	1	0	In.-1; P.-1	Anerobic strept.	Hy.-2	27	0	0	26	0

TABLE IV—*Continued*

Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Lower Urinary Tract					Upper Urinary Tract					
			Sys.	Dias.		Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Bladder	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
9	56	7	150	110	0	0	3	0	In.-1; P.-1	*Strept. hem.*	Bl.-1	25	0	Bl.-1	24	*Strept. hem.*
10	45	2	146	90	0	0	1	0	In.-2; P.-1; B.-3	*B. coli*	Hy.-2; Bl.-1; P.-1; B.-1	25	*B. coli*	0	23	0
11	38	5	122	84	0	0	1	0	In.-2;	*B. proteus;* enterococcus	0	32	Enterococcus	Ptosis	29	0
12	57	4	138	78	0	2	3	180	P.-1; In.-1; B.-1	*Strept. hem.;* anerobic strept.	Hy.-1; Bl.-1; P.-1	42	*Strept. hem.;* anerobic strept.	0	22	0
13	51	3	170	100	1	0	3	0	In.-1; P.-1	0	Hy.-1; Hy. ureter	26	0	0	24	0
14	51	8	130	70	0	0	0	30	In.-1	*B. coli;* enterococcus	Hy.-2; Bl.-2	4	0	0	30	0

TABLE V

Patients with Abnormalities Confined to the Lower Urinary Tract

Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Lower Urinary Tract					Upper Urinary Tract					
			Sys.	Dias.		Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Bladder	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
1	65	0	190	90	0	2	0	0	0	Anerobic gram neg. bac.	0	29	0	0	22	0
2	68	14	180	90	1	3	3	150	In.-3; P.-3; B.-1	*Staph. aur. hem.*	0	20	0	0	20	0
3	68	7	128	90	Cataracts	3	3	135	In.-3; P.-3; B.-3	Gram pos. rods	Ureters not catheterized					
4	46	0	120	80	0	2	0	0	In.-1; P.-1	*B. coli*	0	28	0	0	27	0
5	49	2	210	134	Corneal scars	2	1	0	In.-1; P.-1	0	0	32	0	0	25	0
6	51	0	120	75	0	0	0	0	In.-1; P.-1	0	0	38	0	0	43	0
7	62	10	135	80	0	3	3	60	In.-1; P.-1; B.-1	*Strept. hem.*	0	33	0	0	22	0
8	63	0	210	105	1	3	0	0	In.-1; P.-1	Anerobic strept.	0	26	0	0	25	0
9	53	8	142	80	—	3	3	0	In.-1; P.-1	Anerobic strept.	0	26	0	0	25	0
10	60	3	190	100	1	0	1	600?	In.-3; P.-3 B.-3	*B. coli*	0	24	0	0	28	0

TABLE V—*Continued*

						Lower Urinary Tract					Upper Urinary Tract					
Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Bladder	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
			Sys.	Dias.												
11	62	2	205	105	1	0	1	100	P.-1	Entero-coccus	0	22	0	0	24	0
12	45	4	190	90	0	1	1	0	In.-1; P.-1	0	0	32	0	0	29	0
13	55	10	160	90	0	0	2	0	In.-1; P.-1	0	0	23	0	0	25	0
14	37	7	150	90	0	3	3	0	In.-1; P.-1	Anerobic gram neg. bac.	0	37	0	0	35	0
15	62	7	158	90	Cata-racts	0	3	30	0	0	0	24	0	0	23	0
16	70	0	134	82	1	0	0	0	In.-1	0	0	24	0	0	30	0
17	61	0	138	78	Cata-racts	3	0	90	0	0	0	17	0	0	20	0
18	52	2	140	90	0	3	3	0	0	0	0	42	0	0	38	0
19	51	7	136	90	0	0	1	0	In.-1; P.-1	Entero-coccus	0	27	0	0	25	0
20	58	1	170	100	0	0	0	0	In.-1; P.-1	*Strept. hem.*	0	22	0	0	18	0
21	48	2	130	80	0	3	3	180	In.-2	0	0	20	0	0	20	0
22	58	1	204	104	1	3	3	0	In.-2	0	0	20	0	0	20	0
23	47	2	170	90	1	0	0	90	In.-1; P.-1	Entero-coccus	0	34	0	0	33	0
24	55	4	160	100	1	3	0	0	In.-1	*Strept. hem.*	0	31	0	0	31	0
25	43	7	120	80	0	0	3	0	In.-1; P.-1	0	0	30	0	0	32	0

TABLE VI

Patients with Normal Urinary Tracts

Case No.	Age	Pregnancies	B.P. Average		Retinal Arteriosclerosis (Grade)	Lower Urinary Tract					Upper Urinary Tract					
			Sys.	Dias.		Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (c.c.)	Bladder	Culture	Right Ureter and Kidney	P.S.P. % 30 min.	Culture	Left Ureter and Kidney	P.S.P. % 30 min.	Culture
1	44	1	138	80	0	0	0	0	0	0	0	23	0	0	28	0
2	48	4	170	80	1	0	0	0	0	0	0	20	—	0	20	—
3	46	4	120	85	0	0	0	0	0	0	0	41	0	0	33	0
4	46	4	119	80	0	0	0	0	0	0	0	27	0	0	8	0
5	70	8	130	70	0	0	0	0	0	0	0	26	0	0	20	0
6	47	1	130	88	0	0	0	0	0	0	0	31	0	0	31	0
7	53	4	150	80	1	0	0	0	0	0	0	28	0	0	28	0

arteries was found in five patients; in three of the patients its severity was grade 1; in one patient, grade 2; and in one patient, grade 3. Cataracts were present in two patients.

Table IV: *Patients with Bilateral Normal Kidney Function and Unilateral Urologic Lesions* (group IV). Fourteen patients fell in this group. Eight of these were judged to have hypertension. In five the unilateral disturbance was an active infection whereas in the remaining cases the evidence pointed to a residuum of probable past involvement. One patient had a stone in the ureter. Four had retinal arteriosclerosis, grade 1, and one, grade 2; two had cataracts.

Table V: *Patients with Abnormalities Confined to the Lower Urinary Tract* (group V). Thirteen of the 26 patients who had involvement of the lower urinary tract only had hypertension. None of these had advanced sclerosis of the retinal arteries. Nine were judged to have grade 1 sclerosis. Three had cataracts, one corneal scars, and the retina of one was not examined.

Table VI: *Patients with Normal Urinary Tracts* (group VI). Only seven patients in this series of 84 diabetic women were completely free of pathologic changes in the urinary tract. Two of these were classified as hypertensives, but there was an increase in the systolic pressures only. Both of these had evidence of a slight sclerosis of the retinal arteries.

Stricture of the Urethra, Cystocele and Residual Urine. It seemed reasonable to suppose that the presence of stricture of the urethra, cystocele

TABLE VII

Summary of the Incidence of Hypertension, Retinal Arteriosclerosis and Upper Urinary Tract Infection in the Various Groups

Groups	Average Age	Number of Patients	With Hypertension	Advanced Retinal Arteriosclerosis	Active Upper Tract Infection	Evidence Suggesting Past Infection
I. Bilateral reduction of kidney function.....	54	6	5	4 (cat. 2)	3	3
II. Unilateral reduction of function with bilateral lesions.....	58	16	13	5 (cat. 3, glau. 1)	13	2
III. Normal kidney function bilaterally with bilateral lesions..	55	15	8	2 (cat. 2)	9	6
IV. Normal kidney function bilaterally with unilateral lesions..	55	14	8	1 (cat. 2)	5	3
V. Involvement of lower urinary tract only.....	55	26	13	0 (cat. 3)	—	—
VI. Urinary tract entirely normal..	51	7	2	0	—	—

and residual urine either alone or in combination might be conducive to bacterial growth, particularly when the urine contained sugar which might act as a favorable culture medium. Such factors might operate in much the same manner as prostatic obstruction in the male in the production of ascending infection. However, of the 51 patients who had various degrees of involvement of the upper urinary tract, caused chiefly by infection, only 17 had any degree of stricture of the urethra as compared with the presence of stricture in 16 of 26 patients who had only lower urinary tract lesions. It is to be added, however, that many of the patients in the lower urinary tract group were placed there solely because they had a urethral narrowing. Similar statements likewise apply to the occurrence of cystocele and residual urine. Many of the patients who were unable to empty their bladders completely had 'diabetic neuritis' so this failure might have had a neurogenic basis.

Pregnancies. Since during pregnancy there is often sufficient pressure on the ureters to produce hydronephrosis and since 'pyelitis' of pregnancy is relatively frequent, data on the number of pregnancies were collected. Obviously it was impossible to get any accurate information on the incidence of toxemia of pregnancy. In looking over the tables it did not appear worthwhile to make any minute analysis of the influence of pregnancy on urinary infections. Only 10 of the women had not borne children. Of these 10 barren women five had definite infections of the upper urinary tract. It is possible that pregnancy was responsible for hydronephrosis or hydroureter in some of our patients. This seems unlikely, however, especially in those cases in which there was associated blunting of the calyces.

Bacteriology

Patients with Upper Urinary Tract Involvement. (Groups I, II, III, IV.) Fifty-one patients had abnormalities in the ureters or renal pelves or in kidney function as measured by the 'phthalein test, either on one or both sides. Of these, 34 had active infections in the bladder and in one or both renal pelves, which were quite regularly associated with hydronephrosis, hydroureter, narrowing of the ureter or stone. In some instances these occurred singly, but more frequently in combination. Of those which showed a growth of but a single organism these bacteria were found in the following instances: *Bacillus coli,* 14; *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*), 1; *Bacillus aerogenes capsulatus,* 1; *Staphylococcus aureus hemolyticus,* 1; *Bacillus proteus,* 1; *Streptococcus hemolyticus,* 2; *Enterococcus,* 3; anerobic streptococcus, 2; *Bacillus alkalescens,* 1; and an anerobic gram negative gas-producing bacillus, 1. When there was a double bacterial invasion the following combinations were found: *Bacillus coli* and *Enterococcus,* 3; *Enterococcus* and gram negative gas-producing bacillus, 1; *Bacillus coli* and *Proteus morgani,* 1; *Enterococcus* and *Bacillus aerogenes capsulatus,* 1; and *Streptococcus hemolyticus* and anerobic streptococcus, 1.

Patients with Lower Urinary Tract Involvement. Fourteen of the 26 patients in this group had pus in the bladder urine sediment and bacteria on culture. The following instances of infection were found: *Bacillus coli,* 2; *Enterococcus,* 3; anerobic gram negative gas-producing bacillus, 2; *Streptococcus hemolyticus,* 3; *Staphylococcus aureus hemolyticus,* 1; gram positive rods, 1; and anerobic streptococcus, 2. It appeared that when the *Bacillus coli* was the invading organism the upper urinary tract was more frequently involved.

Findings in the Pelves and Ureters of the Patients not Showing Active Infection. There were 17 patients who were placed in the groups who showed some manifestation of an abnormality of the upper urinary tract but who did not have active infection. Only one of the patients was placed in those groups because she had a reduction of renal function alone. The remainder showed some degree of distortion of the calyces, hydronephrosis, hydroureter, narrowing of the ureter, stone or a reduction of function. These abnormalities were occasionally found only singly but frequently they were present in various combinations. The right side appeared to be involved in a greater number of instances and somewhat more extensively. We realize that these abnormalities might have been of little or no clinical significance and that probably they were evidences of a past infection or possibly of some mechanical interference, but since these abnormalities were so frequently found in the patients who had active infections they were regarded as definite disturbances.

Partial Control Series. Since our diabetic patients showed infection and pathological changes of the urinary tract so commonly and since there was no report of a similar study of non-diabetic women with which we were acquainted, it seemed necessary that some sort of control be attempted. As we did not think it justifiable to subject normal women to complete urologic examinations the bladders of 24 women who were undergoing weight reduction in the obesity clinic were catheterized in the urologic department. The urine was examined for pus and bacteria immediately and then cultured. Twelve of them had a few leukocytes in the sediment; none had marked pyuria. Nine had a few bacteria in the smear and one was classified as having 'many'. Only six had a completely sterile urine; the bacterial flora was much the same as in the diabetic women who had involvement of the lower urinary tract. Three of the control women harbored *Bacillus coli* in the bladder urine.

Discussion

The assembled material may be discussed under two distinct headings: first, the incidence of infection of the urinary tract in diabetic women and secondly, the rôle of infection of the upper urinary tract in these cases in the production of arterial hypertension.

There is little available literature on infection of the urinary tract of normal healthy women. Leishman [1] found seven of 100 people (50 men

and 50 women) to have *Bacillus coli* in the urine. We studied the catheterized specimens of urine from 24 unselected, obese, non-diabetic women; none of them was found to have marked pyuria and only one had numerous bacteria in the smear. Our findings, therefore, make it appear probable that diabetic women do have a higher incidence of infection of the urinary tract than would be expected in normal women. Further it is questionable whether a few leukocytes and bacteria constitute a clinical infection, as it is well known that both the male and female urethras normally harbor bacteria, but the presence of bacteria and leukocytes in the upper urinary tract must be regarded as evidence of infection. Sharkey and Root [2] found 35 cases, 20 women and 15 men, in 196 consecutive necropsies with purulent infection of the urinary tract. They believed, however, that 74 per cent of these were of hematogenous origin caused by infection elsewhere in the body, and therefore their study is not comparable to ours. They commented on the susceptibility of diabetic patients to urinary infection, the chronicity of such infections, and the paucity of clinical symptoms which accompany this involvement. A recent unpublished study from the same clinic, by Baldwin and Root,[3] which we have been given the privilege of examining and quoting, contains data from 143 additional necropsies on diabetic patients. In this group 21 per cent had infections (all types) of the upper urinary tract. The authors compare this incidence with large, general necropsy statistics, which probably included a small percentage of diabetics, in which the incidence of infection of the upper urinary tract was but 4 per cent.

From the standpoint of hypertension we believe that our group of patients are representative of any group of diabetic women who would be attending an out-patient clinic. Many of them were obese. They had been under our observation for varying periods, some of them for as long as 20 years. Their ages varied from 36 to 79 years. Under such circumstances a high incidence of hypertension would be expected. Beck and his co-workers [4] made a survey in our clinic on hypertension in non-diabetic, obese subjects and in early diabetic patients, most of whom were women. Hypertension was found in 50 per cent of the diabetic patients and in 31 per cent of the obese patients. The average age of the diabetic patients, however, was 11 years greater. The incidence of well-established hypertension was about the same in the two groups and occurred at about the same age.

In the present series, of 33 patients—those belonging to the normal group and those who had involvement of the lower urinary tract only (Groups V and VI)—slightly less than 50 per cent had hypertension. The degree of retinal arteriosclerosis did not exceed grade 1 in any patient. Such a grade was present in 11 instances. In Groups III and IV, of the 29 patients who had unilateral or bilateral lesions but with normal function bilaterally, slightly more than 50 per cent had hypertension. Seven of the patients in these groups had retinal arteriosclerosis, grade 1; two had grade

2 and one grade 3. In Groups I and II, of the 22 patients who had reduced renal function on one or both sides, 18, or 82 per cent, had hypertension. An ophthalmologic examination was made of 21 of these patients. Five of them had cataracts and one had glaucoma so that the retina could not be seen. Of the remaining 15, three had grade 3 retinal arteriosclerosis, three grade 2, and five grade 1.

Pus cells and bacteria were found in 34 of the 51 patients who had involvement of the upper urinary tract either on one or both sides. This finding was associated in the majority of cases with distortion of the calyces, as determined by retrograde pyelograms, hydronephrosis, hydroureter, narrowing of the ureter and a reduction of function either unilaterally or bilaterally. These changes, of course, were found in various combinations. Some of the patients who did not show infection at the time of the examination showed similar changes which might be interpreted as residua of healed lesions.

The observations of a number of investigators make it appear that chronic pyelonephritis may be responsible for sclerosis of the vessels of the kidney, reduction of kidney function, and changes in the entire vascular system with hypertension. Longcope and Winkenwerder [5] and Longcope [6] observed a group of 22 patients with chronic bilateral pyelonephritis over a period of several years and noted the development of arterial hypertension and retinal arteriosclerosis in 12. This occurred chiefly in women between the ages of 15 and 30. They believed that pyelonephritis often had its inception in acute pyelitis or more rarely an acute pyonephritis during childhood. They commented that their patients did not commonly seek medical attention until symptoms of renal failure appeared. In a recent monograph on pyelonephritis and its relationship to vascular lesions and arterial hypertension Weiss and Parker [7] presented data on 100 patients with pyelonephritis. The tables in their article contained clinical and pathologic information on 72 cases. Of the 52 who had bilateral pyelonephritis 39 had hypertension and 30 died of uremia. Twenty had unilateral chronic pyelonephritis, twelve of whom had hypertension and four of whom died of uremia (they died during an attack of bilateral acute pyelonephritis). Forty-nine of the 72 patients were women. These patients represented a wide age variation. The renal arterioles of the patients who had hypertension showed a high grade of productive endarteritis and hyperplastic arteriosclerosis and a few showed necrotizing arteriolitis. Of the patients who had normal blood pressures the renal arterioles were involved, but to a lesser extent, and none of them had necrotizing arteriolitis. They believe that pyelitis practically never occurs unaccompanied by pyelonephritis. A complete bibliography accompanies their monograph.

It therefore appears that pyelonephritis commonly progresses to the point where there is sufficient encroachment upon the kidney parenchyma to produce renal failure. If this be the case, then we ask why diabetic pa-

tients, if they frequently have infection of the upper urinary tract, do not develop uremia more commonly. Renal failure, in our experience, is relatively unusual as a cause of death in diabetics. We have, however, observed a few instances in which diabetic women have died of uremia and hypertension which were clearly associated with pyelonephritis. Warren [8] reports that in Joslin's Clinic from August 1922 to 1930, only 4.4 per cent of 1,294 deaths of patients who were diabetic were caused by nephritis. In the present group only three patients (the first three in Group I) were found to have any considerable degree of disturbance of kidney function as measured by the 'phthalein test. It is conceivable, however, that there may be infection of the upper urinary tract (chronic pyelonephritis) which progresses very slowly. Such an infection might cause sclerosis of the small vessels of the kidney and reproduce the Goldblatt [9] experiment by causing a gradual throttling down of the renal circulation and subsequent ischemia, without serious damage to the kidney parenchyma within the lifetime of the patient.

Summary and Conclusions

Complete urologic examinations have been carried out on 84 unselected diabetic women between the ages of 36 and 79 without regard for complaints that would suggest trouble in the urinary tract. Some degree of involvement of the upper urinary tract was found in 51; abnormal findings in the lower urinary tract were found in 26; only seven had what was regarded as a completely normal urinary tract. The patients were grouped in accordance with the involvement of the lower or upper urinary tracts and those who had a disturbance of the upper urinary tract were subgrouped with respect to the renal function as determined by the 'phthalein test. A comparative study of the incidence of hypertension and of retinal arteriosclerosis was made in the various groups.

Leukocytes and bacteria were found in the renal pelves of 34 of the patients either on one or both sides. This finding was usually associated with other abnormalities of the urinary tract such as distortion of the calyces, hydronephrosis and narrowing of the ureter.

A variety of pathogenic bacteria was found, but the *Bacillus coli* predominated in those whose upper urinary tract showed infection. In the patients who had bacteria only in the bladder the *Bacillus coli* was less frequently found; otherwise, the bacterial flora was about the same as was found in the upper urinary tract group.

The patients who were found to have infections in the urinary tract frequently had no symptoms or at least none that would be differentiated from diabetic symptoms either past or present. It is believed that infections of the urinary tract in diabetic women often go undiagnosed because of the difficulty in the interpretation of the examination of urine from the human female. Catheterization under strict aseptic precautions is often justified.

Of 22 patients who had bilateral lesions or a reduction of function as measured by the 'phthalein test either on one or both sides 18 (82 per cent) had hypertension. Of 29 patients who had normal kidney function bilaterally but who had unilateral or bilateral lesions in the calyces, pelves or ureters, slightly more than 50 per cent had hypertension. Of thirty-three patients who had only abnormalities of the lower urinary tract or who had normal urinary tracts slightly less than 50 per cent had hypertension. Retinal arteriosclerosis was more frequent and was of a higher grade in those patients who had a reduction of kidney function either on one or both sides.

An extreme reduction of kidney function was found bilaterally in only three patients. The low incidence of renal failure as a cause of death in diabetic patients is commented upon.

It is suggested that in diabetic women there is frequently a slowly progressive pyelonephritis which may or may not produce a reduction of kidney function either bilaterally or unilaterally. This infection may in some cases be responsible for or contribute to the hypertension which is so common in older diabetic women.

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THE HYPERTENSINASE CONTENT OF PLASMA OF NORMAL, HYPERTENSIVE AND NEPHRECTOMIZED DOGS*

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THE pressor substance, hypertensin, was demonstrated by Braun-Menendez, Fasciolo, Leloir, and Muñoz [1, 2, 3, 4] of this Institute in the renal venous blood of ischemic kidneys and was shown to be identical with the pressor substance produced by the in vitro incubation of renin with blood globulins (hypertensin precursor) and unlike other known pressor substances. They concluded, therefore, that hypertensin is the pressor substance responsible for hypertension due to renal ischemia. Braun-Menendez and his collaborators [2, 3, 4, 5] likewise described a substance, hypertensinase, which destroys or inactivates hypertensin. Its distribution in the body, a method of its extraction from tissues, and a biological method for its assay have been described. The present report describes in detail certain modifications of the method of Fasciolo et al.[5] to make it more applicable for the quantitative determination of hypertensinase in plasma and reports on the concentration of hypertensinase in plasma of normal, hypertensive, and nephrectomized dogs.

METHODS

Arterial blood was withdrawn from dogs using the usual precautions to avoid hemolysis; 0.1 volume of a 3.8 per cent solution of sodium citrate was used to prevent coagulation and the amount of dilution due to the citrate was taken into account in the calculation of the volume of plasma used for the determination of hypertensinase. After centrifugation, the amount of hemolysis in the plasma was determined roughly by means of the benzidine test. The color developing was compared with that produced by dilutions of packed red blood cells varying between 1 : 2500 and 1 : 40,000. Plasmas containing more hemolysis than one part in 5000 were discarded. Since Fasciolo et al.[5] found 80 to 120 units of hypertensinase in 1 c.c. of washed red blood cells, the amount present in a 1 : 5000 dilution would be only approximately 0.02 unit which lies well outside the limit of error of the method.

All tubing, pipettes, etc., used in the preparation of solutions, were autoclaved or boiled. A testing solution was made up fresh as follows: standard hypertensin, 1 unit; M/2 NaH_2PO_4 (pH 7.4), 0.5 c.c.; merthiolate (Lilly), 0.2 c.c.; distilled water ad 8.0 c.c. To 8 c.c. of the testing solution in seven

* Received for publication December 13, 1941.
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test tubes were added exactly 1.5, 1.0, and 0.5 c.c. of undiluted plasma, and 1.5, 1.0, and 0.5 c.c. of plasma diluted 1 to 4 with distilled water. The seventh tube was used as a control. The volume of each tube was made up to 10 c.c. with distilled water. At first, a second control tube consisted of 8 c.c. of the testing solution and 2 c.c. of plasma the hypertensinase content of which had been destroyed by changing the pH to 3.9 for 20 minutes at 37° C. and then neutralizing. This was later omitted, however, because the same value was always obtained as in the control tube using water instead of plasma.

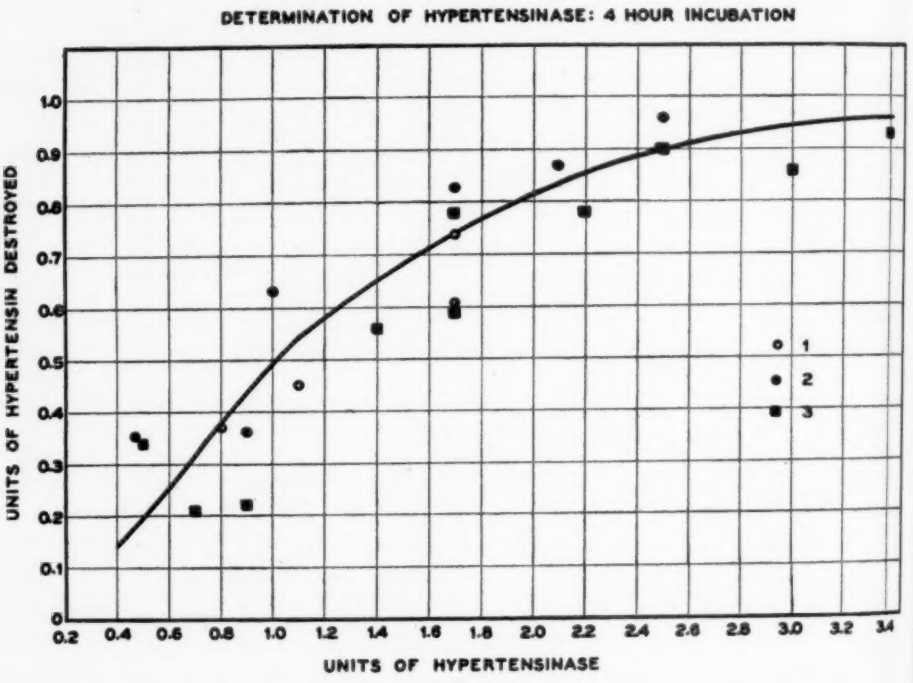

FIG. 1. The destruction of hypertensin by hypertensinase during four hours of incubation at 37° C. Dots, circles, and squares represent experiments on different days.

The tubes were incubated in a water bath for two hours at 37° C. and then placed in boiling water for 10 minutes to destroy the hypertensinase present. The solutions were injected intravenously into dogs of about 10 kilos anesthetized with chloralose or nembutal. The amount of hypertensin present in each tube was determined according to the method of Braun-Menendez, Fasciolo, Leloir, and Muñoz.[6] The amount of hypertensin destroyed by the hypertensinase was calculated by subtracting the amount found from 1.0 unit which was the amount of hypertensin originally present in each tube. From the amount of hypertensin destroyed, the amount of hypertensinase present was calculated from the curve of figure 2.

Results

Two and Four Hour Incubation Curves. Fasciolo et al.[5] defined the unit of hypertensinase as the amount which in a volume of 10 c.c. destroys 0.5 unit of hypertensin in four hours at a temperature of 37° C. A solution of hypertensinase was prepared from liver as described by Fasciolo et al., and the amount present was determined by the method described on three occasions by taking serial dilutions containing 0.4 to 3.4 units of hypertensinase. One series of tubes was incubated for four hours and the other for two. The

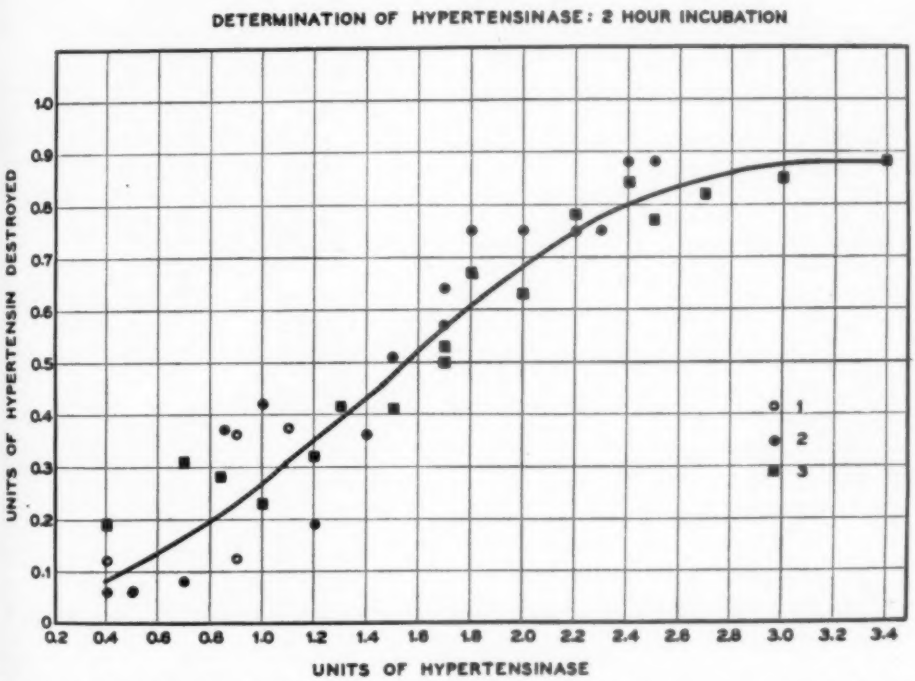

FIG. 2. The destruction of hypertensin by hypertensinase during two hours of incubation at 37° C. Dots, circles, and squares represent experiments on different days.

validity of the four hour curve of Fasciolo et al. was confirmed (figure 1). From the number of units present as determined by the four hour incubation, and from the number of units of hypertensin destroyed by incubating for two hours, a two hour curve was constructed (figure 2). In this way, the same unit of hypertensinase as defined by Fasciolo et al. has been retained and the time of incubation reduced to two hours.

Hypertensinase Content of Plasma. The hypertensinase content of plasma of 10 normal dogs, four dogs nephrectomized 48 hours previously, and five dogs rendered hypertensive by constriction of the renal artery was determined. The results are shown in table 1. Normal values for hypertensinase lay between 1.5 and 3.9 units per c.c. of plasma. Similar values were found in the nephrectomized and hypertensive dogs.

TABLE I

The concentration of hypertensinase in the plasma of normal dogs, dogs nephrectomized 48 hours previously, and dogs made hypertensive by renal ischemia.

Group	Dog No.	Units of Hypertensinase per c.c. Plasma	Blood Pressure (mm. Hg)
Normals	1	2.5	—
	2	2.8	—
	3	2.2	—
	4	2.4	—
	5	3.9	—
	6	2.4	—
	7	1.6	—
	8	2.1	—
	9	3.4	—
	10	2.2	—
Nephrectomized 48 hours previously	1	2.2	—
	2	1.2	—
	3	1.4	—
	4	2.2	—
Hypertensive by renal ischemia	1	1.9	260
	2	2.0	190
	3	1.9	160
	4	1.8	200
	5	2.4	190

SUMMARY AND CONCLUSIONS

1. Certain modifications have been introduced into the method of Fasciolo, Leloir, Muñoz, and Braun-Menendez [5] for the determination of hypertensinase in plasma. The method is described in detail.

2. The plasma of normal dogs contains between 1.5 and 3.9 units of hypertensinase per cubic centimeter.

3. The hypertensinase content of plasma of dogs nephrectomized 48 hours previously and of dogs rendered hypertensive by renal ischemia is normal.

The author is indebted to Prof. B. A. Houssay and Dr. E. Braun-Menendez for their constant advice and suggestions and to Dr. L. F. Leloir and Dr. J. M. Muñoz for their preparation of the solution of hypertensin used in these experiments.

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THE SENSITIVITY TO HYPERTENSIN, ADRENALIN AND RENIN OF UNANESTHETIZED NORMAL, ADRENALECTOMIZED, HYPOPHYSECTOMIZED AND NEPHRECTOMIZED DOGS *

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In 1898 Tigerstedt and Bergmann [1] discovered a pressor substance in normal kidneys to which they gave the name renin. This substance had a prolonged pressor effect when injected intravenously into animals, successive injections had a diminishing pressor action (tachyphylaxis), and it was not found in organs other than the kidneys. Their findings have been widely confirmed by subsequent investigators. With the development of a method of inducing hypertension experimentally in animals by Goldblatt, Lynch, Hanzal, and Summerville [2] and with the resultant evidence that this renal hypertension was apparently due to a humoral mechanism,[3, 4] the rôle played by renin in experimental hypertension has recently been the subject of extensive study by many. Kohlstaedt, Helmer, and Page [5] found that purified preparations of renin had no constrictor action when perfused in Ringer's solution through the vessels of an isolated rabbit's ear, but that when perfused with blood proteins ("reninactivator") a strong constrictor action was obtained. This has been confirmed by others.[6, 7] Following a series of experiments by Houssay and his collaborators on the pressor and constrictor properties of venous blood of ischemic kidneys (recently reviewed by Houssay [8]), Braun-Menendez, Fasciolo, Leloir, and Muñoz [9, 10, 11, 6] of the same laboratory in 1939 discovered a pressor substance, hypertensin, in the venous blood of ischemic kidneys. In its chemical, physical, and pharmacological properties it was identical with the pressor substance produced by the in vitro incubation of renin with blood globulins (hypertensin precursor; hypertensinogen). It differed in its properties from adrenalin, pitressin, tyramin, and urohypertensin. Hypertensin is rapidly destroyed by hypertensinase which is widely distributed throughout the body and which has no action on renin or on precursor.[6, 12] Page and Helmer [13] independently described the production of the same pressor substance which they called angiotonin, by the interaction of renin and blood colloids. The term "renin-activator" applied to the blood colloids seems inappropriate, however, since from the studies of Braun-Menendez et al.[9, 10, 14] it is apparent that renin is an enzyme and that the globulin fraction of the blood is the substrate on which it acts. Kohlstaedt and Page [15] and Leloir, Muñoz, Fasciolo, and Braun-Menendez [16] subsequently demonstrated the liberation of renin from the venous blood of

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perfused kidneys. The relationship between renin and experimental renal hypertension, therefore, seems established.

There is a considerable body of evidence indicating that there is a close relationship between the pituitary and adrenal glands and hypertension and that the normal kidney exerts a protective action against the development of experimental renal hypertension. One of us (B. A. H.[8]) has recently summarized the present knowledge of these relationships. The purpose of this communication is to report a study made of the sensitivity to hypertensin, adrenalin, and renin of normal, adrenalectomized, hypophysectomized, and nephrectomized dogs in an attempt to clarify further the relationship which exists between these organs and renal hypertension.

Methods

Unanesthetized normal, adrenalectomized, hypophysectomized, and nephrectomized dogs weighing between 7 and 12 kilos were injected intravenously with 2 units of hypertensin, 10 gamma of adrenalin (Parke Davis) and 2 c.c. of a solution of hog renin in the order stated. The blood pressure was recorded by a cannula in the femoral artery (novocaine being used as a local anesthetic) connected to a mercury manometer. The animals were usually quiet during the experiment.

Hypertensin was prepared according to the method of Muñoz, Braun-Menendez, Fasciolo, and Leloir[11]; 0.18 c.c. contained 1 unit which is the amount as defined by Braun-Menendez, Fasciolo, Leloir, and Muñoz,[17] which gives rise to an elevation of blood pressure of 25 to 30 mm. Hg in a 10 kilogram chloralosed dog. Renin was prepared from the cortex of hogs' kidneys according to the method of Braun-Menendez, Fasciolo, Leloir, and Muñoz[6] and contained 1 unit in 0.025 c.c. The unit of renin as defined by Leloir, Muñoz, Braun-Menendez, and Fasciolo[18] is the amount which when incubated at 37° C. for two hours with an excess of precursor (6 to 8 c.c. of hypertensinase-free bovine plasma) is capable of forming 0.5 unit of hypertensin.

Dogs were bilaterally nephrectomized under ether anesthesia by the lumbar or abdominal route. The adrenals were removed in two stages at least two weeks apart using the lumbar approach. After the removal of the second adrenal, 20 grams of sodium chloride alone or complemented in part with sodium citrate were administered daily by stomach tube. The experiment was performed on the adrenalectomized and nephrectomized dogs 40 to 48 hours after operation. All animals used showed definite symptomatic evidence of adrenal or renal insufficiency. Hypophysectomy was performed by the temporal approach, the animals being used one month to three years after the operation.

Venous blood was withdrawn before adrenalectomy and again about 40 hours after adrenalectomy, some three to four hours before the dogs were injected with the pressor substances. The indirect method of Leloir, Muñoz,

Braun-Menendez, and Fasciolo [18] was used to determine the concentration of renin in the blood, and the method of Muñoz, Braun-Menendez, Fasciolo, and Leloir [11] was used to determine the concentration of precursor in the plasma.

Results

The effect of the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. of a solution of hog renin on the blood pressure of nine normal unanesthetized dogs, 12 dogs 40 to 48 hours after adrenalectomy, six hypophysectomized dogs, and nine dogs 40 to 48 hours after nephrectomy is summarized in table 1. The number of animals used was too small for statistical analysis.

1. Normal Dogs. Following the intravenous injection of 2 units of hypertensin, the blood pressure rose on an average 35 ± 13 mm. Hg with a range of 18 to 48; after 10 gamma of adrenalin, 30 ± 9 mm. Hg with a range between 13 and 45; and after 2 c.c. of renin, 51 ± 15 mm. Hg ranging between 30 and 78 mm. The upper limit of the normal response, therefore, was considered to be 48 mm. Hg to hypertensin, 39 mm. to adrenalin, and 66 mm. to renin. In general, there was a parallelism in the blood pressure response to hypertensin and adrenalin. In only one dog (No. 5) was the response to renin less than that to hypertensin. The duration of the pressor action of renin noted in four cases lasted on the average 37 minutes and in no instance exceeded one hour.

2. Adrenalectomized Dogs. The initial blood pressure of the adrenalectomized dogs was considerably lower than in the normal controls, and all dogs were moderately weak and apathetic. Despite this, there was a normal or even increased sensitivity to hypertensin in all but one case (No. 5) and to adrenalin a variable response with possibly a tendency to a slight decrease in sensitivity. The response to renin was variable. In dogs 2, 3, 4, 6, 9, and 10, the response to renin was normal and to hypertensin normal or above normal. In dogs 1, 7, 8, and 12, there was a normal or increased sensitivity to hypertensin, indicating a normal reactivity of the vessels, but a definitely diminished pressor response to renin in comparison with the pressor effect of hypertensin. Since the pressor action of renin is due to the hypertensin formed from its interaction with precursor,[5, 9] it seemed of importance to ascertain the concentration of precursor in the blood. It will be noted (table 2) that precursor was markedly reduced in the arterial blood approximately 40 hours after adrenalectomy as compared with values obtained before ablation of the second adrenal in dogs 7, 8, 11, and 12 in which the response to renin was decreased, and normal in dogs 9 and 10 in which the response to renin was normal. Dogs 5 and 11 were in frank insufficiency and shock and sensitivity to all three drugs was decreased. The duration of action of renin in these adrenalectomized dogs was usually shorter than in the controls. There was only a rough correlation between

TABLE I

The sensitivity of *unanesthetized* normal, adrenalectomized, hypophysectomized, and nephrectomized dogs to the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. (80 units) of a solution of hog renin in the order stated.

Group	Dog No.	Wt.	Initial Pressure	Elevation of Blood Pressure after:			Duration of Action of Renin
				2 Units Hypertensin	10 Gamma Adrenalin	2 c.c. Renin	
		Kg.	mm.Hg	mm.Hg	mm.Hg	mm.Hg	min.
Normal dogs	1	8.5	135	45	41	78	—
	2	8.5	125	30	25	48	—
	3	8.6	150	40	30	65	—
	4	10.5	170	27	22	50	—
	5	9.0	180	40	28	33	—
	6	12.5	160	30	36	40	53
	7	8.5	200	40	35	65	45
	8	10.0	120	18	13	30	30
	9	8.5	130	48	45	48	19
	Average			35	30	51	37
	Probable error			±13	±9	±15	±13
Adrenalectomized 48 hours previously	1	9.0	80	65	60	38	—
	2	8.0	98	52	40	65	—
	3	9.0	100	32	20	40	—
	4	11.0	130	35	12	45	45
	5	9.0	60	18	25	20	10
	6	9.0	70	50	25	40	10
	7	10.0	95	50	18	20	22
	8	10.0	75	37	20	28	23
	9	10.5	90	38	18	50	40
	10	10.0	25	40	16	40	25
	11	10.0	60	26	16	25	15
	12	8.5	60	50	36	40	9
	Average			41	26	38	22
	Probable error			±12	±13	±12	±12
Hypophysectomized 1 month to 3 years previously	1	8.0	128	42	40	45	—
	2	9.0	140	44	44	50	—
	3	12.0	140	48	35	55	—
	4	8.0	130	30	30	40	—
	5	9.0	135	24	−5	30	—
	6	9.0	130	35	30	40	14
	Average			37	29	43	—
	Probable error			±8	±16	±8	
Nephrectomized 48 hours previously	1	11.0	148	53	40	82	—
	2	11.0	135	52	25	80	—
	3	10.0	125	30	25	50	—
	4	10.5	180	30	25	60	180
	5	11.0	120	30	32	85	165
	6	9.0	130	65	55	120	60
	7	12.0	180	48	30	88	77
	8	12.5	160	22	10	38	38
	9	10.0	130	60	75	85	80
	Average			43	35	77	100
	Probable error			±15	±18	±23	±53

the initial level of the blood pressure and the sensitivity to the pressor substances.

3. Hypophysectomized Dogs. The sensitivity of six unanesthetized hypophysectomized dogs to the injection of hypertensin, adrenalin, and renin appeared to be entirely normal (table 1).

4. Uremic Dogs. Four out of nine of the dogs nephrectomized 40 to 48 hours previously (No. 1, 2, 6, and 9) showed an increase in sensitivity to hypertensin, and three of these four dogs (No. 1, 6, and 9) to adrenalin. The basic cause of the hyper-reactivity of the vessels to these drugs is not apparent. The same dogs (No. 1, 2, 6, and 9) showed a greater increase in pressure than normal following the injection of renin, due at least in part to the hypersensitivity of the vessels to the hypertensin formed by the action

TABLE II

The concentration of precursor and renin in the plasma of unanesthetized dogs before and 48 hours after adrenalectomy.

Dog No.	Units of Precursor per c.c.		Units of Renin per c.c.	
	Before	After	Before	After
7	0.26	0.09	None	None
8	0.18	0.03	"	"
9	0.19	0.25	"	"
10	0.21	0.22	"	"
11	0.22	0.12	"	"
12	0.40	0.09	"	"

of renin on the precursor of the blood. In addition, two other dogs (No. 5 and 7) showed an increase in sensitivity to renin. The pressor effect of renin was notably prolonged in four of five of the dogs in which it was determined.

5. Anesthetized Dogs Nephrectomized One to Three and One-Half Hours Previously. The sensitivity to hypertensin, adrenalin, and renin was determined in nine dogs nephrectomized one to three and one-half hours previously. It was necessary to use chloralose anesthesia (10 c.c. of a 0.8 per cent solution per kilo intravenously) because of the restlessness of the animals so soon after operation. A control series consisted of nine normal chloralosed dogs whose kidneys were explored but not manipulated. The results are seen in table 3. Chloralose anesthesia did not diminish the sensitivity to hypertensin, adrenalin, or renin, nor was the duration of the pressor action of renin altered. In the recently nephrectomized animals there was no increase in sensitivity to either hypertensin or adrenalin, nor in the majority of the animals to renin. In three (No. 3, 7, and 8), however, the pressor response to the injection of renin was decidedly greater than normal, and in two (No. 2 and 8) the pressor effect lasted two and two and a quarter hours respectively. In two dogs (No. 8 and 9), the amount of precursor in the blood before and three hours after operation was unchanged.

Discussion

The observations on adrenalectomized dogs indicate that the vessels reacted normally or almost normally in response to injections of hypertensin and adrenalin until the advent of terminal shock. The sensitivity to injections of renin was normal in six cases and reduced in six cases, which is in accord with the observations of Williams, Diaz, Burch, and Harrison [19] and of Friedman, Somkin, and Oppenheimer.[20] Remington, Collings, Hays, and Swingle [21] noted a normal response of adrenalectomized dogs to large

Table III

The sensitivity of *chloralosed* normal and recently nephrectomized dogs to the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. (80 units) of a solution of hog renin in the order stated.

Group	Dog No.	Wt.	Initial Pressure	Elevation of Blood Pressure after:			Duration of Action of Renin
				2 Units Hypertensin	10 Gamma Adrenalin	2 c.c. Renin	
		Kg.	mm.Hg	mm.Hg	mm.Hg	mm.Hg	min.
Normal dogs 1 to 5 hours after exploration of kidneys	1	10.0	130	25	32	20	10
	2	9.0	150	40	66	60	27
	3	8.0	165	25	30	40	10
	4	9.0	170	36	10	60	10
	5	9.0	105	50	24	40	30
	6	7.0	160	48	40	40	30
	7	9.0	140	44	30	20	40
	8	9.0	120	62	66	40	20
	9	11.0	160	35	16	45	60
	Average			41	35	41	26
	Probable error			±11	±19	±13	±16
Nephrectomized 1 to 3½ hours previously	1	12.5	130	48	50	55	24
	2	13.0	130	30	45	60	120
	3	12.0	120	36	34	70	58
	4	11.0	130	50	36	44	33
	5	7.0	140	28	82	40	43
	6	10.5	170	27	40	40	26
	7	10.5	130	62	43	75	28
	8	8.5	110	64	57	78	135
	9	13.5	120	58	52	43	43
	Average			45	49	56	56
	Probable error			±14	±13	±14	±39

doses of renin but a diminished response to small doses beginning almost immediately after the withdrawal of cortical extract. The dose used by us may have been too large to detect the early appearance of diminished sensitivity. In four cases there was a normal response to hypertensin but a diminished response to renin. In these cases the reactivity of the vessels may be considered normal. In these same cases, but not in two others in which the sensitivity to hypertensin and renin was normal, the concentration of precursor in the plasma was found to be distinctly reduced, which probably is a factor not only in the diminished pressor response to renin, but also in

the short duration of its action, since Leloir, Muñoz, Braun-Menendez, and Fasciolo [18] have shown that the amount of hypertensin formed by the action of a given amount of renin depends upon the amount of precursor present. In two dogs in which the pressor response to renin was normal the concentration of precursor in the plasma was found to be normal. These studies give no clue as to the cause of the diminution in the concentration of precursor. No renin was found in the blood of any of the dogs 40 to 48 hours after adrenalectomy by the indirect method of Leloir, Muñoz, Braun-Menendez and Fasciolo,[18] which is capable of detecting 0.2 unit of renin or even less with accuracy. Although the possibility still exists despite this negative finding, it seems unlikely that the cause of the reduction of precursor was the liberation of renin by the kidney such as occurs in certain shock-like conditions.[22]

When the adrenalectomized animals were in profound shock, such as dogs 5 and 11 and several others not included in this series, the sensitivity to hypertensin and renin was uniformly depressed, and that to adrenalin variable. Elliot [23] reported a marked pressor response to large doses of adrenalin in cats in terminal adrenal insufficiency. Armstrong, Cleghorn, Fowler, and McVicar [24] likewise observed in cats in adrenal insufficiency a good pressor effect from the injection of adrenalin in doses similar to those used by us.

It seems plausible to assume that following adrenalectomy two factors are involved in the diminished sensitivity to injections of renin. First, at a late stage of adrenal insufficiency, the vessels lose their normal reactivity not only to renin but to hypertensin and at a later stage to adrenalin as well. Second, in certain animals but not in all (four of six of the dogs tested in this series) there is a clear reduction in the concentration of precursor in the blood so that the amount of hypertensin capable of being formed by the renin injected is reduced. Whether this factor plays a rôle in the fall of blood pressure of hypertensive animals after adrenalectomy can only be surmised at this time.

In the hypophysectomized animals no alteration from normal was noted in the sensitivity to hypertensin, adrenalin, or renin. Williams, Diaz, Burch, and Harrison [19] observed an increased sensitivity to renin in hypophysectomized rats. We are unable to explain the difference in our results. It is probable, however, that such factors as species variations and anesthesia account for the differences, or, as the authors suggest, the lower initial pressure of the rats after hypophysectomy. The initial pressure of our dogs was normal. Our results throw no light on the dampening effect of hypophysectomy on hypertension from renal ischemia.

Recently nephrectomized (one to three and one-half hours) dogs reacted normally to injections of hypertensin, adrenalin, and, in the majority of instances, to injections of renin. In three instances, however, the pressor action of renin was greater and in two it lasted much longer than in normal dogs. Forty-eight hours after nephrectomy distinct differences were ob-

served in that several dogs showed a clear increase in sensitivity to hypertensin and to adrenalin. There was likewise an increase above normal in the pressor response to renin in the majority of the dogs, which is in accord with the observations of other investigators.[1, 25, 26, 27, 28, 29] The duration of the pressor action of renin was more than twice as long as in the normal control dogs. At least three factors appear to account for the hypersensitivity to and the prolonged action of renin in the uremic dogs: (*a*) The vessels of the dogs 48 hours after nephrectomy are more sensitive than normal to the injection of the pressor substances used. (*b*) Given enough time, the amount of hypertensin formed by a given amount of renin depends upon the concentration of precursor present. Muñoz, Braun-Menendez, Fasciolo, and Leloir [11] demonstrated that 48 hours after nephrectomy the concentration of precursor is increased. Therefore, in these dogs the increase in the concentration of precursor undoubtedly plays a rôle in the heightened and prolonged pressor effect of renin. (*c*) It has been shown by Houssay, Braun-Menendez, and Dexter [22] that in dogs nephrectomized 48 hours previously renin after its injection intravenously persists in detectable amounts in the blood for two to three hours or more, whereas in normal dogs it disappears usually within an hour. The velocity of the reaction between renin and precursor to form hypertensin depends on the concentration of renin present.[18] Since renin persists for a longer time in the blood of these animals, the rate at which hypertensin forms is increased, thereby playing a part in the increased height to which the blood pressure rises as well as to the prolongation of the pressor action.

Summary

1. The sensitivity of unanesthetized normal, adrenalectomized, and nephrectomized (uremic) dogs to 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. of a solution of hog renin has been determined.

2. Forty-eight hours after bilateral adrenalectomy, the sensitivity to hypertensin and adrenalin was usually normal unless terminal shock appeared. The sensitivity to renin was sometimes normal and sometimes reduced. The decrease in the sensitivity to renin at a time when the vessels were reacting normally to hypertensin was associated in four instances with a fall in the concentration of hypertensin precursor (hypertensinogen) in the plasma.

3. Dogs hypophysectomized one month to three years previously reacted normally to the injection of hypertensin, adrenalin, and renin.

4. Chloralosed dogs recently nephrectomized reacted normally to hypertensin and adrenalin and usually to renin. In three of nine dogs the pressor effect of renin was greater, and in two of nine it lasted distinctly longer than in the normal controls.

5. Unanesthetized dogs nephrectomized 48 hours previously frequently were hypersensitive to hypertensin, adrenalin, and renin. The duration of action of renin was usually markedly prolonged. The causes of the hypersensitivity to renin in these dogs are discussed.

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THE DESTRUCTION AND ELIMINATION OF RENIN IN THE DOG*

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Tigerstedt and Bergmann [1] described a pressor substance, renin, which is found in kidney but not in other organs and which has a prolonged pressor effect when injected intravenously. Kohlstaedt and Page [2] showed that purified renin had no vasoconstrictor action when perfused through a rabbit's ear but that it became active when mixed with blood colloids. This has been corroborated by others.[3] Braun-Menendez, Fasciolo, Leloir, and Muñoz [4, 5, 3] identified a pressor and vasoconstrictor substance, which they called hypertensin, in the venous blood of ischemic kidneys and showed that the same substance could be obtained in vitro by incubation of renin with blood globulins. This was confirmed independently by Page and Helmer [6] who have called the pressor substance "angiotonin" and the blood globulins "renin-activator."

According to Muñoz, Braun-Menendez, Fasciolo, and Leloir,[7] the mechanism of renal hypertension might be summarized as follows: Renal ischemia determines the secretion of renin.[8, 9] This protein is an enzyme which acts on a blood globulin (hypertensin precursor) and gives rise to a substance (hypertensin) which produces vasoconstriction. Another enzyme "hypertensinase" which destroys hypertensin is present in blood and tissues.

Because of the important rôle played by renin in the development of experimental hypertension, a study has been made of the mechanisms by which renin is eliminated or destroyed by the body. Three general methods of investigation have been utilized: (*a*) search for renin in the urine after its intravenous injection; (*b*) study of the disappearance of renin from the blood after its injection into normal animals and animals deprived of certain organs; and (*c*) search for a substance in blood which would neutralize or destroy renin.

Methods

Hog renin was prepared according to the method of Braun-Menendez, Fasciolo, Leloir, and Muñoz [3] and contained approximately 100 units per c.c., one unit of renin being the amount which when incubated for two hours at 37° C. with hypertensinase-free precursor is capable of giving rise to the formation of 0.5 unit of hypertensin.[10] The renin content of plasma was determined by the direct method of Leloir, Muñoz, Braun-Menendez, and Fasciolo.[10]

The renin content of urine was determined in most instances using the same method as for plasma. In a few instances urine was previously ex-

* Received for publication December 13, 1941.
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tracted for renin by acidifying to pH 4.5, adding ammonium sulphate (400 gm. per liter), filtering, dialyzing the precipitate in a cellophane sac overnight in the icebox, redissolving the contents of the sac in distilled water, neutralizing and filtering. This method of extraction was tested by adding renin to urine. Little or no apparent loss of renin occurred by the process of extraction.

In the determination of renin in the urine by the method used, which consists in the incubation for two hours at 37° C. of variable amounts of urine with an excess of hypertensinase-free precursor, two causes of error may exist. Another pressor substance may exist in the urine or the pressor

TABLE I

Excretion of renin in the urine after the intravenous injection of variable amounts of renin into normal anesthetized or unanesthetized dogs.

Dog	Wt.	Anesthesia	Amount of Renin Injected (1 c.c. 100 U.)	Diuresis		Renin in Urine		Renin Recovered
				Volume	Hours of Observation	Presence	Amount in Units	
	kg.		c.c.	c.c.				%
1	15	None	2	4	1	No	—	—
2	10	Chlor.	2	?	1	No	—	—
3	12	None	2	?	1	No	—	—
4	13	None	2	150	2	No	—	—
5	17	None	2	57	1.5	Traces	—	—
6	18	None	2	18	1.5	No	—	—
7	16	Amytal	3	13	1.5	Yes	18	6
8	15	Chlor.	4	143	2	Yes	34	8.5
9	12	None	4	57	1	Yes	?	?
10	13	Chlor.	5	103	2	Yes	36	7.2
11	14	None	5	148	2	Yes	140	28
12	14	None	10	76	1.5	Yes	?	?
13	13	None	10	28	2	Yes	420	42

substance formed by incubation of urine and precursor may not be hypertensin. If a control tube prepared by mixing urine and precursor without incubating gave no pressor response, no extraneous pressor substance existed in the urine. On the other hand, the pressor substance formed was identified as hypertensin if it was destroyed by incubation with hypertensinase prepared from red cells or liver.[11]

Dogs were used in all experiments. Nephrectomy was performed by the lumbar or abdominal approach using ether or chloralose (10 c.c. of a 0.8 per cent solution per kilo intravenously) as an anesthetic. Hepatectomy was performed on chloralosed dogs by making an Eck fistula by means of a Payr's tube between the portal vein and left renal vein, both kidneys being removed, or by tying the hepatic artery and ligating one by one the lobes of the liver. With this technic, hepatectomy is practically complete and studies from this Institute show that no hepatic function remains. Evisceration was performed on chloralosed dogs by removal of all abdominal viscera with the exception of the liver, the lobes of which were ligated. After hepatectomy

TABLE II

Concentration of renin in blood after the injection of 2 c.c. (80 units) of hog renin intravenously into *unanesthetized* normal, recently nephrectomized and uremic dogs.

Group	Dog	Wt.	Units of Hypertensin in 8 c.c. of Plasma					
			Before	After				
				5 min.	30 min.	60 min.	120 min.	180 min.
		kg.						
Normals	1	14.0	None	0.64	0.04	0.08	None	None
	2	8.0	None	0.48	0.09	0.09	None	None
	3	9.0	None	0.75	None	None	None	None
	4	9.0	None	1.89	None	None	None	None
	5	9.0	None	0.39	None	None	None	None
	6	11.0	None	1.14	0.18	None	None	None
Nephrectomized 3 to 4 hours previously	1	9.0	None		0.80	0.12	None	None
	2	14.5	None		0.18	0.06	None	None
	3	14.0	None	0.82	0.50	0.08	None	None
	4	11.5	None	0.53	0.29	None	None	None
Nephrectomized 48 hours previously	1	10.5	None		0.23	0.36	0.21	0.21
	2	12.0	None		0.36	0.24	0.15	0.11
	3	9.0	None			0.33	0.20	0.13
	4	12.5	None		1.01	0.42	0.22	0.03
	5	12.5	None		0.38	0.09	0.19	None
	6	10.0	None		1.36	0.30	0.08	None
	7	14.0	None		1.29	0.62	0.45	0.13
	8	14.5	None		0.82	0.20	0.18	0.16

(Results expressed as units of hypertensin formed after two hours incubation at 37° C. with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

and evisceration, a direct transfusion from another chloralosed dog was given before injecting renin.

In transfusing recently nephrectomized dogs with uremic blood and uremic dogs with normal blood, the chloralosed recipient dog was placed on a scale and bled half of his calculated blood volume. The blood volume was assumed to be 7 per cent of the body weight. Transfusion from the donor dog, also anesthetized with chloralose, was made by means of a short rubber tube between the carotid artery of the donor and the jugular vein of the recipient. Enough blood was transfused to restore the original weight of the recipient. Two or three such bleedings and transfusions were thus performed, so that at the end of the third 87.5 per cent of the blood of the recipient was calculated to be donor blood.

For the perfusion of isolated organs, either the heart-lung preparation of Starling or an artificial pumping system was used. The heart-lung preparation of dogs was made in the classical manner. The defibrinated blood was allowed to circulate for approximately one hour or more before beginning the perfusion of the isolated organ in order to eliminate the vasoconstrictor substance (Spätgift) which is present in defibrinated blood.

For perfusion of the liver, the hepatic artery was cannulated and received blood from the arterial side of the circuit. The portal vein received blood from the circuit distal to the peripheral resistance. Kidneys were perfused by two methods, one with the heart-lung preparation and the other with a system of Dale-Schuster pumps and a Hooker oxygenator. In the latter, defibrinated blood which had circulated through the heart-lung preparation for an hour or more was used.

Results

The Excretion of Renin in the Urine. By means of a catheter introduced in the urinary bladder, urine was collected before and at half hour intervals after injection of variable amounts of renin into the jugular vein of unanesthetized or anesthetized dogs (table 1). In six experiments 2 c.c. of renin were injected and in only one could traces of renin be recognized in the

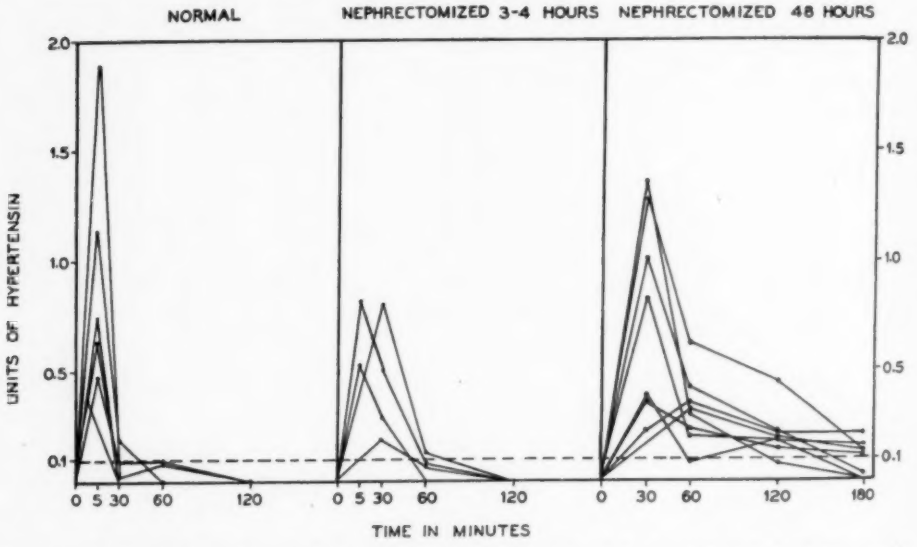

Fig. 1. Concentration of renin in blood after the injection of 2 c.c. (80 units) of hog renin intravenously into *unanesthetized* normal, recently nephrectomized, and uremic dogs.

(Results expressed as units of hypertensin formed after two hours incubation at 37° C. with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

urine. The injection of greater amounts was followed in every instance by the renal excretion of renin. The amount of renin recovered from the urine was from 6 to 42 per cent, being roughly proportional to the amount injected. The second half hour sample of urine contained most of the renin excreted and none was present two hours after the injection. These results have been reported elsewhere.[12]

The Disappearance of Injected Renin from the Blood of Unanesthetized Normal and Nephrectomized Dogs. Two c.c. of renin were injected into

TABLE III

Concentration of renin in blood after the intravenous injection of hog renin into chloralosed normal, recently nephrectomized, nephrectomized and hepatectomized, eviscerated, and uremic dogs.

(Results expressed as units of hypertensin formed after two hours incubation at 37° C. with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

Group	Dog	Wt.	Amount of Renin Injected	Volume of Plasma Used in Testing	Units of Hypertensin in Plasma							
					Before	After						
						5 min.	15 min.	30 min.	60 min.	120 min.	180 min.	300 min.
		kg.	c.c.	c.c								
Normal intact dogs	1	16.0	3.0	6.0	None		0.80	0.21	None			
	2	15.0	4.0	6.0	None		0.60	0.08	0.04			
	3	13.0	5.0	6.0	None		1.30	0.26	None			
	4	15.0	2.0	6.0	None	0.57		0.10	0.04			
	5	15.0	2.0	6.0	None	0.73		None				
Normals; kidneys explored	1	11.5	2.0	8.0	None			0.48	0.26	0.10	0.04	
	2	10.0	2.0	8.0	None	1.97	1.45		0.30	None	0.16	
	3	8.0	2.0	8.0	None	0.82	0.70	0.64	None	0.45	0.66	
	4	9.0	2.0	8.0	None	0.54	0.74	1.23	0.52	0.33	None	
Nephrectomized 1 to 3 hrs. previously	1	13.0	2.0	8.0	None			0.69		0.12	None	
	2	9.0	2.0	8.0	None			0.71	0.59	0.26	None	
	3	11.0	2.0	8.0	None			0.80	0.27	None	None	
	4	7.0	2.0	8.0	None			0.31	0.09	None	None	
Nephrectomized and hepatectomized	1	16.0	2.0	8.0	None	0.42			0.49	0.09	0.07	
	2	18.0	4.0	4.0	None	0.85		0.56	0.58	0.10	0.02	
Eviscerated	1	20.0	3.0	4.0	None	1.00			0.43	0.24	0.03	
	2	23.0	3.0	6.0	None	0.66			0.50	0.36	0.13	
Nephrectomized 48 hrs. previously	1	7.0	3.0	6.0	None	2.68			1.12	0.41	0.41	0.38
	2	7.5	3.0	6.0	None	2.26			0.24	0.16	0.14	0.07
	3	7.0	3.0	6.0	None	1.85			0.36	0.19	0.19	0.11

the jugular vein of six control dogs whose kidneys were explored but not manipulated three or four hours previously under ether anesthesia, four dogs nephrectomized three or four hours previously, and eight dogs nephrectomized 48 hours previously. The results are shown in table 2 and figure 1. Renin usually disappeared from the blood stream in less than 30 minutes in the control group, in about an hour in the recently nephrectomized dogs, and small but definite amounts persisted for two to three hours in the majority of the dogs nephrectomized 48 hours previously. Differences in the amount of renin present in the first 15 or 30 minutes are not significant and are attributable to inadequate amounts of precursor used in incubating with the blood samples containing such large quantities of renin. These experiments indicate that in nephrectomized dogs there is a delay in the disappearance of the injected renin, especially marked if nephrectomy is per-

formed 48 hours previously. Because of obvious difficulties in working with unanesthetized animals, the problem was pursued using chloralosed dogs.

The Disappearance of Injected Renin from the Blood of Anesthetized Normal, Nephrectomized, Hepatectomized and Eviscerated Dogs. In this group of experiments all animals were anesthetized with chloralose (10 c.c. of a 0.8 per cent solution per kilo) intravenously. Renin was injected as in

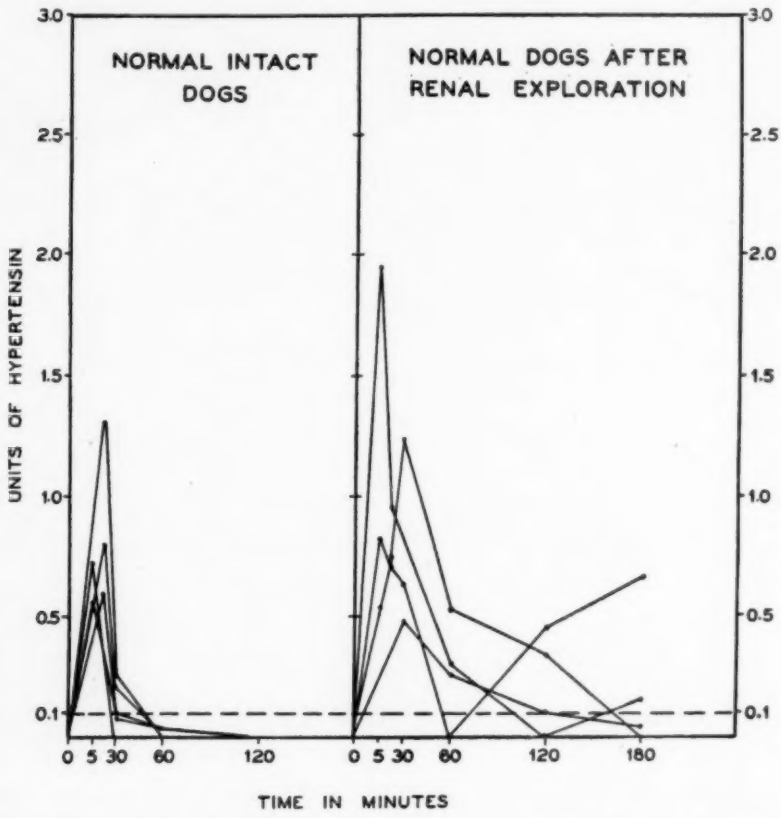

FIG. 2. Concentration of renin in blood after the intravenous injection of hog renin into normal chloralosed dogs and chloralosed dogs whose kidneys had been explored but not manipulated.

(Results expressed as units of hypertensin formed after two hours incubation at 37° C. with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

the preceding experiments to five control intact dogs, four dogs whose kidneys were explored but not manipulated, four dogs nephrectomized one to three hours previously, three dogs nephrectomized 48 hours previously, two dogs hepatectomized and nephrectomized immediately before the injection of renin, and two dogs eviscerated immediately before the injection of renin. The results are shown in table 3 and figures 2 and 3.

In anesthetized intact dogs renin disappeared from the blood in about 30 minutes but great irregularities were observed in the disappearance of renin from the blood of the anesthetized dogs whose kidneys were explored. In two instances there were actual increases in the concentration of renin which were far beyond the error of the method. Such increases were never observed in any of the nephrectomized animals. One of these dogs (No. 3) presented the picture of shock with low blood pressure and sighing respira-

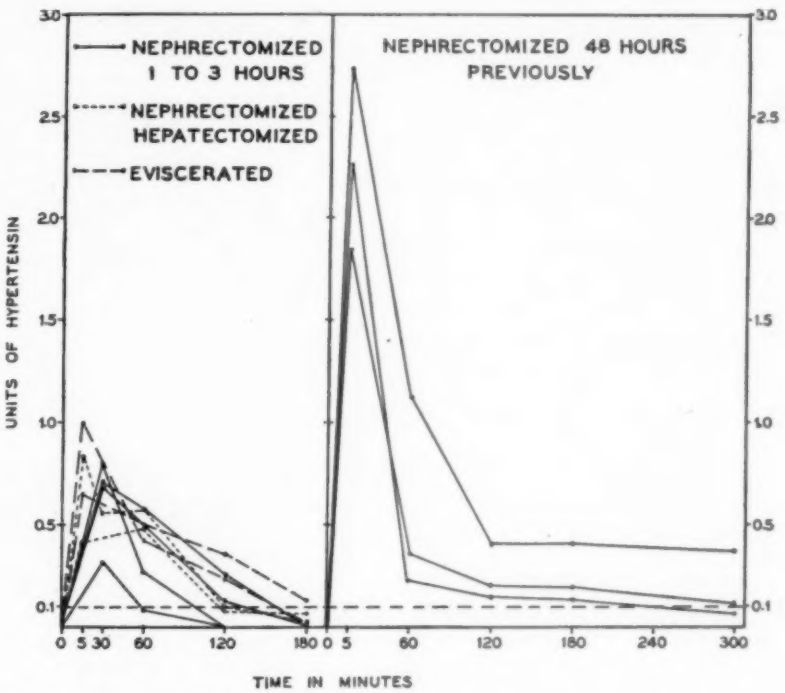

FIG. 3. Concentration of renin in blood after the intravenous injection of hog renin into chloralosed recently nephrectomized, nephrectomized and hepatectomized, eviscerated, and uremic dogs.

(Results expressed as units of hypertensin formed after two hours of incubation at 37° C. with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

tions. The other (No. 4), however, appeared in good condition. Both dogs 1 and 2 had low pressures without showing increased amounts of renin in the blood. The striking difference in the disappearance of renin from the blood of this group of dogs and the normal anesthetized or unanesthetized dogs is presumably a consequence of the operation under chloralose anesthesia leading to impaired renal function or shock, and manifested by the production of renin or by its faulty destruction or elimination.

In dogs nephrectomized one to three hours previously, renin disappeared from the blood before the second hour, and in those nephrectomized 48

hours previously between three and four hours or more. As compared with the disappearance curves in the unanesthetized dogs, there was a slight delay in the disappearance of renin from the blood of chloralosed dogs. Immediately after nephrectomy and hepatectomy, and immediately after evisceration, renin disappeared at the same rate as in the dogs recently nephrectomized (table 3 and figure 3).

From these experiments it may be concluded that under certain circumstances the kidney may produce renin in sufficient amounts to be detected in the blood by the method employed, that chloralose anesthesia delays somewhat the time of disappearance of injected renin from the blood but that mechanisms other than those exerted directly by the kidneys, liver and other abdominal viscera are of importance in the destruction of renin by the body. Indeed renin disappears rapidly from the blood in eviscerated and in recently nephrectomized dogs. The rate of disappearance is slightly but definitely prolonged when compared with that of the intact control dogs. On the other hand, in the uremic anesthetized and unanesthetized dogs there is a great delay in the disappearance of injected renin. Two possibilities present themselves to explain the fact that the ability of the body to destroy renin is much reduced in dogs nephrectomized 48 hours previously and only slightly reduced in recently nephrectomized or eviscerated dogs: (*a*) that the normal kidney secretes a substance which neutralizes or destroys renin or its action and that this substance persists in the blood for some hours after nephrectomy; (*b*) that renin is destroyed by the tissues of the body but that in uremia there is a disturbance of this metabolic activity on the part of the tissues. The following experiments were devised to investigate these possibilities.

Attempts to Demonstrate the Ability of Blood Withdrawn from Various Sites to Destroy or Inhibit the Action of Renin. Hog renin (0.25 c.c.) was added to 80 c.c. of citrated blood obtained from the carotid artery of a chloralosed dog. Merthiolate (3.5 c.c.) was added to prevent bacterial growth. The blood was incubated for three hours at 37° C. Samples of blood were withdrawn at five minutes, one hour, two hours, and three hours and their renin content estimated. There was no diminution in the amount of renin present in any of the samples, thereby indicating that renin was not adsorbed to red cells or destroyed by contact with whole blood during this interval.

By the method described, no destruction of renin or of its action by plasma or whole blood from the jugular vein, carotid artery, suprahepatic vein, and renal vein of a normal etherized dog could be detected. Similarly negative results were obtained with serum obtained from the hepatic veins of two livers after perfusion with the heart-lung preparation for 28 and 42 minutes respectively and from the venous blood of four kidneys perfused 40, 113, 35, and 60 minutes respectively. No destructive action on renin could be demonstrated by whole defibrinated blood obtained from the renal vein

of one kidney perfused for 30 minutes. The amount of renin in whole blood, plasma, or serum after two hours of incubation was exactly the same as in the sample withdrawn immediately after the addition of renin.

The Disappearance of Injected Renin from the Blood of a Recently Nephrectomized Dog Transfused with Uremic Blood and from the Blood of a Uremic Dog Transfused with Normal Blood. In order to ascertain if the slow disappearance of renin from the blood of dogs 48 hours after nephrectomy was due to an alteration in the normal metabolic destruction of renin by the tissues or the absence of some neutralizing or destructive

TABLE IV

Concentration of renin in blood after the injection of 3 c.c. (120 units) of hog renin intravenously into uremic dogs transfused with normal blood and recently nephrectomized dogs transfused with uremic blood.

(Results expressed as units of hypertensin formed after two hours incubation at 37° C. with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

Group	Dog	Wt.	Calculated Amount of Circulating Donor Blood	Units of Hypertensin in 6 c.c. of Plasma					Condition Symptomatically
				Before	After				
					5 min.	1 hour	2 hours	3 hours	5 hours	
		kg.	%							
Uremic dogs with normal blood	1	7.0	87.5	None	1.56	0.56	0.56	0.51	0.46	Severe uremia
	2	7.0	87.5	None	1.36	0.53	0.34	0.23	0.05	Mod. uremia
	3	8.0	87.5	None	1.26	0.19	0.09	0.12	None	Mild uremia
Recently nephrectomized dogs with uremic blood	1	8.0	75.0	None	1.52	0.52	0.08	0.05	None	Good
	2	7.3	87.5	None	2.26	1.11	0.25	0.09	0.02	Good
	3	6.5	75.0	None	1.37	0.28	None	None	None	Good

factor present in normal blood, the blood of three normal dogs nephrectomized 48 hours previously was transfused into three normal dogs nephrectomized a few minutes previously, and the blood of three normal dogs was transfused into three dogs nephrectomized 48 hours previously. By the method described the recently nephrectomized dogs were calculated to have approximately 75, 75, and 87.5 per cent uremic blood respectively, and the uremic dogs 87.5 per cent each of normal blood. Three c.c. of renin were injected intravenously into each and its rate of disappearance noted for five hours (table 4 and figure 4). Renin disappeared from the blood of uremic dogs with normal blood in three to five hours or more, the time of disappearance seemingly being influenced by the severity of the uremia, and from the blood of recently nephrectomized dogs with uremic blood in less than three hours in each case. It has been concluded, therefore, that the marked

interference with the normal destruction of renin in the uremic dog is due to a disturbance of the destructive action of the tissues in uremia rather than to the absence of some substance which is present in the blood of recently nephrectomized dogs and which disappears 48 hours after nephrectomy.

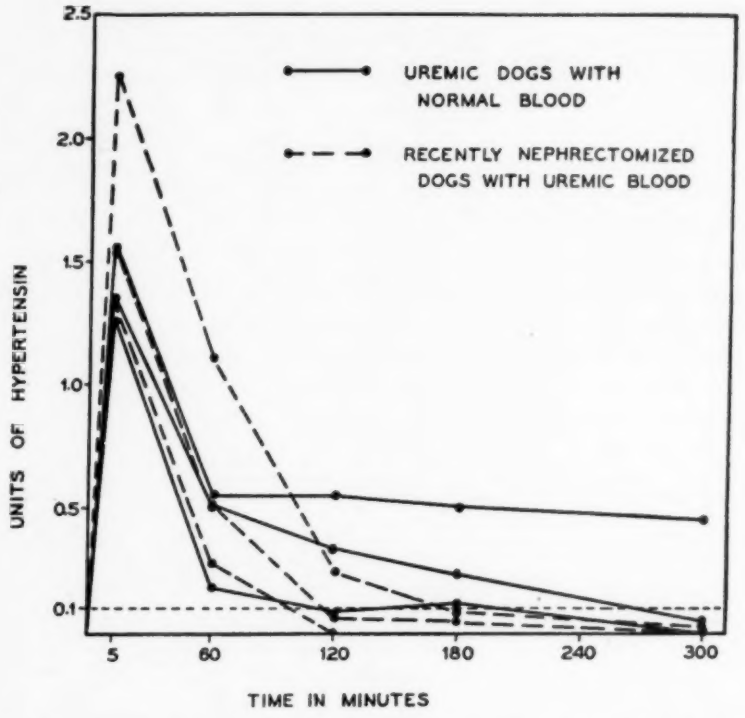

FIG. 4. Concentration of renin in blood after the injection of 3 c.c. (120 units) of hog renin intravenously into uremic dogs transfused with normal blood and recently nephrectomized dogs transfused with uremic blood.

(Results expressed as units of hypertensin formed after two hours incubation at 37° C. with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

DISCUSSION

Considerable evidence exists in the literature that the kidney has a protective action against the renal humoral substance responsible for hypertension from renal ischemia. For a summary of the literature and review of the work done in this Institute, see Fasciolo[13, 14, 15] and Houssay.[16] This protective action is usually not sufficient to prevent the development of hypertension by constricting the renal artery of the opposite kidney, but under certain conditions of stress, the influence of the normal kidney becomes manifest. It is of interest to consider the evidence in the light of the present investigation.

Our observations show that in normal unanesthetized dogs whose kidneys were explored three to four hours previously under ether anesthesia, renin disappeared from the blood stream in less than 30 minutes. In recently nephrectomized dogs it disappeared in about an hour (see table 2 and figure 1). Anesthesia with chloralose delayed somewhat the disappearance of renin, but the same difference existed between normal unoperated dogs and dogs recently nephrectomized. In the former renin disappeared in about 30 minutes, in the latter before the second hour (see table 3 and figure 2). Dogs whose kidneys were explored form a group apart which we shall consider presently. These results indicate that the kidneys play a rôle in the destruction of renin in the body.

The excretion of renin in the urine does not explain the greater rapidity with which renin disappeared from the blood of normal dogs because renin appeared in the urine only when amounts greater than 2 c.c. were injected (table 1). Our observations lend no support to the hypothesis that the normal kidney secretes a substance which neutralizes or destroys renin. We were not able to demonstrate the ability of blood withdrawn from various sites to destroy or inhibit the action of renin, nor did the transfusion of normal blood restore the ability of uremic dogs to destroy renin. Perhaps the kidney metabolizes or neutralizes renin but direct proofs of this action have not yet been given.

Of all the abdominal organs the kidneys are the most active in the destruction of renin because hepatectomized and nephrectomized dogs and eviscerated dogs behave like recently nephrectomized dogs after the injection of renin (figure 3). It is evident, however, that the kidney is not the principal factor in the destruction of renin in the body because this substance disappears from the blood in about one to two hours after its injection into recently nephrectomized dogs. Mechanisms other than those exerted directly by the kidneys, liver, and other abdominal viscera are of importance in the destruction of renin by the body. This destructive action of the tissues is disturbed in uremia as shown by the persistence for three to five hours of small amounts of renin in the blood of dogs nephrectomized 48 hours previously. The more rapid disappearance of renin in normal, recently nephrectomized and eviscerated animals as compared with uremic dogs is not due to the persistence in the blood of some substance neutralizing or destroying renin. This was indicated by studying the rate of disappearance of renin from the blood of uremic animals with approximately 87.5 per cent of normal blood and from recently nephrectomized animals with approximately 75 to 87.5 per cent of uremic blood. Renin disappeared slowly from the uremic dogs with normal blood and rapidly from the recently nephrectomized dogs with uremic blood. Furthermore, no destructive action against renin could be demonstrated in vitro of blood, serum, or plasma obtained from hepatic veins, renal vein, jugular vein, or carotid artery.

Exactly what the bodily mechanisms for the destruction of renin are, outside of its elimination in the urine, we are unable to state. The circulating blood has no apparent destructive action. The abdominal viscera apart from the kidney do not appear to play an important rôle in its destruction. Preliminary and incomplete experiments on the disappearance of renin from a perfusing system of isolated organs including the kidney, liver and muscles (leg) have as yet yielded no information as to the tissue or tissues concerned in its destruction or the manner in which such destruction takes place.

As to the four dogs anesthetized with chloralose whose kidneys were explored, they cannot be considered as normal controls. In two of them, the blood pressure was very low and one presented the picture of shock. The delayed disappearance of renin in this group may be explained by the production of renin by the kidney and possibly also by an inhibition of renal function due to the abnormal conditions created by the chloralose anesthesia and the abdominal operation. This is supported by the observation of dog 3 in which the concentration of renin in the blood actually increased (table 3 and figure 2). The secretion of renin by the kidney in shock may be a mechanism by which the body tends to restore the lowered blood pressure in this condition.

Summary and Conclusions

1. A study has been made of the mechanism by which renin injected intravenously disappears from the blood.

2. After the intravenous injection of 2 to 3 c.c. of a solution of hog renin into normal dogs, it disappears from the blood usually within 30 minutes.

3. After the intravenous injection of the same amount of renin into dogs recently nephrectomized, renin disappears from the blood in one to three hours. The same delay is observed in nephrectomized and hepatectomized and in eviscerated dogs. The kidneys seem then to be the only abdominal organs which play a rôle in the disappearance of renin from the body.

4. Abdominal operation under chloralose anesthesia may be followed by a delay in the disappearance of injected renin. In one dog with the picture of shock, an increase in the concentration of renin in the blood was observed.

5. After the intravenous injection of amounts greater than 2 c.c. of renin, a fraction of it was found in the urine. The excretion of renin in the urine does not seem to be an important mechanism in the disappearance of renin from the body and does not account for the delay observed in recently nephrectomized dogs as compared with normal dogs.

6. No neutralizing or destructive property against renin was demonstrable in blood drawn from the jugular vein, carotid artery, hepatic veins, or renal vein.

7. In uremic dogs there is a slow disappearance of injected renin from the blood. The delay in the disappearance is attributable to an alteration of the destructive action of the tissues rather than to a lack of some substance in normal blood which destroys renin because the disappearance of injected renin from the blood is not faster in uremic dogs with approximately 87.5 per cent normal blood and is not modified in recently nephrectomized dogs with approximately 75 to 87.5 per cent uremic blood.

8. It is concluded that although the kidney seems to have some destructive action, destruction of renin by the tissues is the principal factor in its disappearance from the blood. The mechanism by which the kidney and the body tissues destroy renin has not been demonstrated.

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STUDIES ON THE ETIOLOGY AND SERUM TREATMENT OF ENCEPHALITIS DURING THE EPIDEMIC IN NORTH DAKOTA AND MINNESOTA (1941) *

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We have had opportunity to study the etiology of encephalitis as it occurred during the summer and autumn of 1941 and to observe patients while they were under treatment with the encephalitis antistreptococcic serum.

Clinical Studies

The patients with encephalitis observed in this epidemic presented striking similarities in symptomatology and appearance. Headache, nausea and vomiting with fever were the cardinal symptoms. Patients who had the severe forms of the disease were striking in appearance; not infrequently the patients were irrational, many were lethargic and had lost sphincteric control of the bladder and rectum. Rational patients complained bitterly of severe headache which had failed to respond to the usual medications. These patients at times complained also of vertigo, blurred vision and sore throat. In some cases the headache and nausea were unbearable, and the chief complaints were of weakness, backache and ataxia. The onset of the disease often was abrupt, heralded by chills or chilly sensations and headache. Great variations in the severity of symptoms were frequently evident.

From the onset the local physicians, as well as ourselves, were struck with an unusual odor often present at the bedside of the patient. Examination usually revealed acutely ill patients with flushed faces. Their eyelids often appeared swollen and the conjunctivae were injected. Even petechial hemorrhages were noted. Nystagmus was rare, and in no case was ocular paralysis noted. Various degrees of rigidity of the neck, and even opisthotonos among children, were present. The pharynx and soft palate usually were definitely injected. Usually no neurologic changes were demonstrable, aside from hypoactive reflexes, vertigo and ataxia. Localized spasms and even generalized convulsions were observed in some cases. In two patients bulbar paralysis developed before death.

The urine was consistently normal except for occasional specimens in which traces of albumin were found. In only one case was there evidence of pyelonephritis.

* Received for publication November 27, 1941.
We are indebted to Dr. E. J. Larson, Jamestown, North Dakota, Dr. A. C. Baker, Fergus Falls, Minnesota, and their colleagues and to H. J. Larson, D. V. M., Fergus Falls, Minnesota, for their coöperation.

Blood counts showed an average of about 10,000 to 14,000 white blood cells; however, in classic cases a normal leukocyte count often was obtained. The leukocyte counts ranged from 5,000 to 28,000 cells.

The cellular response in the spinal fluid resembled closely that which occurs in epidemic poliomyelitis and that which characterized epidemic encephalitis during the St. Louis outbreak.[1, 2] In a few cases in which unmistakable symptoms were present the spinal fluid was free from cells. The highest count obtained was 695 cells, the average being 150 cells. Polymorphonuclear cells predominated at the onset, and lymphocytes predominated in the later stages of the disease.

Sections of the brains of patients who died revealed typical lesions of encephalitis (figure 1).

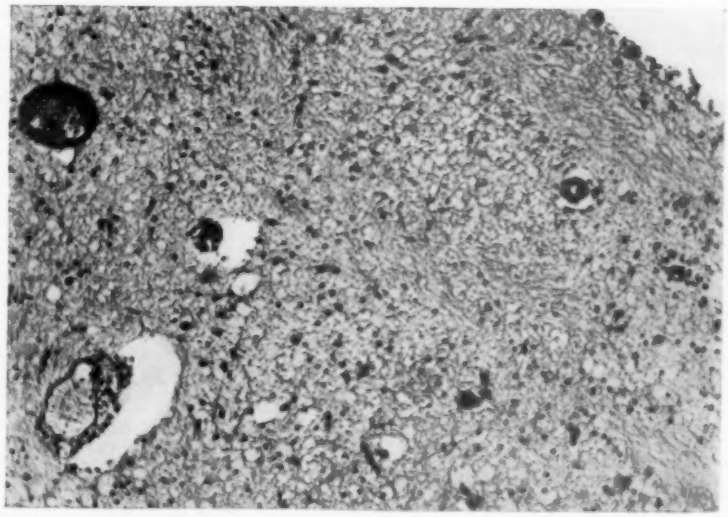

FIG. 1. Perivascular and parenchymatous infiltration and degeneration in the pons of a patient who died (hematoxylin and eosin × 105).

The manner of spread and the incidence of the disease were strikingly like those in epidemic poliomyelitis. No age group appeared to be immune. We saw patients of widely different ages, ranging from five weeks to 82 years. Males, regardless of age, were more often stricken than females, as in epidemic poliomyelitis, the total ratio of males to females being 3 to 1. No females less than five years of age were affected, whereas eight males two and a half years to five weeks of age contracted the disease. There was, of course, no difference in exposure to mosquitoes of female and male babies. Evidence of contact infection, as in encephalomyelitis in horses, was almost wholly lacking. Not once did we encounter more than one instance of the disease in a family group. Patients were observed who gave histories of contact with horses, cattle, sheep or dogs which had symptoms or had died of encephalitis. Mild types of illness, associated often with sore throat, with or

without fever, and severe headache, occurred commonly in one member or more of the family at about the time an undoubted instance of the disease occurred, as well as generally within the epidemic zone. We were impressed by the frequency with which instances of the disease occurred in remote regions, far from main routes of travel. In fact, most of the patients were brought to the hospitals from widely separated farms and gave no history of contact with the disease in human beings.

Bacteriologic and Serologic Studies

On examination of smears of the sediment of centrifugated spinal fluid stained by Gram's stain or by means of a special staining method [3] immediately after spinal puncture, the technicians and physicians at the Jamestown and Trinity Hospitals at Jamestown, North Dakota, found diplococci in 28 of 55 specimens in which search for organisms was made. We have corroborated and extended these observations and have succeeded in isolating streptococci from the spinal fluid (cultured immediately) of patients who had acute forms of the disease (figures 2*a, b, c* and *d*). Examination of speci-

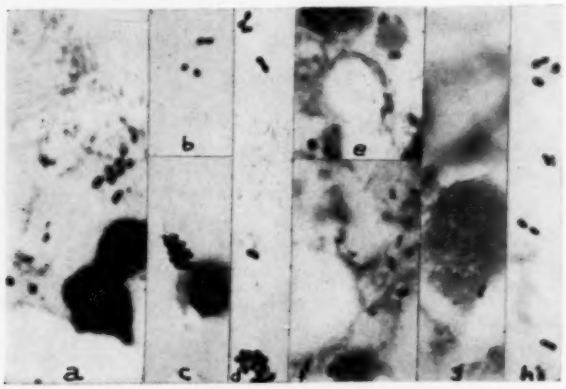

Fig. 2. Diplococci and streptococci in and from the cerebrospinal fluid of four (*a, b, c* and *d*) patients during the acute stage of epidemic encephalitis, and in and from the brain of a patient who died (*e, f, g* and *h*); *a, b* and *c*, in the sediment of the cerebrospinal fluid; *d*, in pure culture in dextrose-brain broth; *e, f* and *g*, in degenerating ganglion cells and the interstitial tissue shown in figure 1; and *h*, in a dextrose brain-broth culture of the emulsion of the brain; *a*, stained by a special method [3]; *b, c, d* and *h*, stained by Gram's method; *e, f* and *g*, stained by a modification of Weigert's method [5] (× 1000).

mens of spinal fluid mailed to us, and reëxamination after storage showed marked reduction in the cell count or complete autolysis of cells, and in no instance were organisms found or isolated.

It should be understood, of course, that the streptococci which have been isolated consistently in studies of poliomyelitis and encephalitis and referred to as such in this paper and in previous papers [1, 2] occur in spinal fluid and lesions chiefly as diplococci or ovoids (figures 2*a, b, c, e, f* and *g*), the former often resembling pneumococci, and in cultures as diplococci and diplococci coupled in chains (figures 2*d* and *h*).

By the use of media containing brain substance, and by other special methods,[4] streptococci which had a specific affinity for the brains of animals in the experimental laboratory and other specific properties were demonstrated or were isolated consistently from nasopharyngeal swabbings, from the stools, from the brain (one case, in which the outcome was fatal), from the spinal fluid of patients, and often from the throats of well "contacts" and well "noncontacts." On intracerebral inoculation of animals with highly diluted (1 to 10,000 to 1 to 100,000,000) cultures of the streptococcus obtained from each of the sources mentioned, the symptoms observed among patients—tremor, muscular spasm, nystagmus, ataxia, excitation, evidence of pain in the head and extremities, lethargy, circumcorneal congestion and subconjunctival hemorrhage, retrobulbar congestion and edema which often produced bulging eyes, cyanotic congestion of the mucous membrane of the trachea and hemorrhagic edema of the lungs sometimes associated with bronchopneumonia (expressive of the respiratory infection in patients)—all have been reproduced. The results in the aforementioned animals resembled closely those obtained in two monkeys, in rabbits, guinea-pigs and mice after inoculation of an emulsion, or filtrate of an emulsion, of the glycerolated brain obtained in one case in which the disease was fatal. This is as should be expected, because the streptococcus was isolated from and demonstrated microscopically in the lesions of this patient's brain, as in the brains of other patients dying of lethargic encephalitis [2, 5] and in the brains of horses that died of equine encephalomyelitis.[6] The glycerolated brain was sent to us by Dr. E. J. Larson of Jamestown, North Dakota. From the brains of animals that succumbed to the inoculation of cultures of the streptococcus, as well as from the brains of those receiving the emulsion or filtrates of corresponding brain tissue (virus), the streptococcus usually was isolated in pure cultures. Moderate to severe congestion and punctate hemorrhages of the brain, without clouding of the meninges, were found consistently in these animals. In the early stages of the experimentally produced disease, as in the disease among patients, the cells in the spinal fluid were chiefly polymorphonuclear, whereas, later, lymphocytes predominated. Diplococci were readily demonstrable in stained smears during the early stages of the experimental disease, but not in the late stages.

The intracutaneous injection of the water-insoluble (euglobulin) fraction of the serum of horses immunized with the streptococci isolated respectively from persons and horses ill with this disease, and with the western type of virus of equine encephalomyelitis, has been uniformly followed by an immediate erythematous-edematous reaction which did not occur, or which occurred to a far less degree, at the sites of control injections. This specific reactivity to the intracutaneous injection of the encephalitis euglobulins persisted for two to three weeks or longer among patients not treated with the serum, whereas among patients who received therapeutic intramuscular injections of the antistreptococcic serum this reactivity of the skin disappeared or became less marked within a half hour to four hours, to recur to a milder

degree if injections of antiserum were discontinued. In all patients tested it had disappeared completely after serum sickness. This was true of human and equine streptococcic euglobulins and the western type of "viral" euglobulin alike.

A specific precipitation reaction was consistently obtained between cleared extracts of nasopharyngeal swabbings and human and equine antistreptococcic sera and three commercial preparations of antiserum produced with the western strain of equine encephalomyelitis "virus." Cutaneous and precipitation tests with the antistreptococcic sera have been made previously, whereas those with the equine antiviral sera have not. By means of the precipitation reaction encephalitic streptococcic antigen was consistently demonstrated in the serum of patients as well as in the serum of horses and other animals ill with symptoms of encephalitis and in the spinal fluid of patients during the acute stage of the disease.

The streptococci isolated from the nasopharynx, stools, brain and spinal fluid of patients, and from the brain of horses and other animals having encephalitis, or which had died from it, were agglutinated specifically by the human and equine antistreptococcic sera, by the equine encephalomyelitis antiviral serum (western type), and by the serum of patients convalescing from encephalitis.

The "encephalitic" type of streptococcus was isolated from the blood and nares of horses, from the brains of sheep, a dog, a hog, chickens, a goose, and a pheasant which were ill or had died with symptoms of encephalitis in the epidemic zone. It was isolated from the brains of wild ducks which were ill and also from the brains and spinal fluid of fish dying in lakes, the water of which yielded the same streptococcus. Moreover, streptococci having "encephalitic" properties were isolated consistently from flies and mosquitoes, from milk, from water of wells in regions in which the disease had occurred, and from the air of rooms occupied by persons or stalls occupied by horses ill with this disease.

Chick-mash medium, dextrose-brain broth, distilled water, and small glass tubes and bottles coated with mineral oil, and tubes with screened ends filled with oiled spun glass or oiled glass beads were exposed to outdoor air in different cities and in the country at ground levels, and at levels as high as 21 stories of a building, at the front of an automobile that was being driven many hundreds of miles in wide areas of the epidemic zone, and at high levels, 1,000 feet or more, in an airplane that was flown by Dr. J. H. Pratt and one of us (Caldwell) over the same routes as those traversed with the automobile while samples at ground level in the epidemic zone had been obtained a few days previously. The " encephalitic" type of streptococcus was consistently isolated and "encephalitic" streptococcic and "viral" antigen were demonstrated by the precipitation reaction in most specimens obtained in stationary and mobile sampling at or near ground level, and the streptococcus was isolated in 60 of 94 cultures made from samples obtained during airplane flights of about 1,000 miles in the epidemic zone. Control samples

of air obtained at ground levels outside the epidemic zone rarely yielded streptococci, and yielded streptococcic antigen in only two of 14 samples.

Moreover, cultures and extracts, in solution of sodium chloride, of dust obtained from filters used in air-conditioning units consistently have yielded the "encephalitic" streptococcus and the "encephalitic" streptococcic and "viral" antigen in large amounts. The details of these experiments and those on the relationship of the streptococci to the so-called virus will be published elsewhere.

Treatment with Serum

The treatment of patients with serum was started during the peak of the epidemic of encephalitis at the two hospitals in Jamestown, North Dakota. Patients who had contracted the disease earlier in the epidemic at Jamestown, as well as those studied throughout the epidemic at Fergus Falls and other smaller outbreaks, who did not receive serum because of unavoidable circumstances, served as controls for members of the serum-treated group. There was no apparent difference in the matter of severity of illness, age, sex and other conditions between the serum-treated group and the nonserum-treated group. Many of the patients received one or another of the sulfonamide compounds, usually sulfapyridine or sulfathiazole. In accord with results of experimental studies,[7, 8, 9] there was little clinical or objective evidence that these drugs exerted beneficial action, either when they were administered alone or when they were given in conjunction with the serum (table 1). Only patients for whom a diagnosis could be made definitely by

Table I

Results of Treatment with Encephalitis Antistreptococcus Serum

Groups	Cases	Average Duration of Fever Days	Deaths	
			Number	Per Cent
Patients not treated with serum who recovered	20	10.9		
Patients treated with serum who recovered	56	7.2		
Patients treated with serum soon after onset of symptoms—first or second day	15	6.3		
Patients treated with sulfonamide compounds only	5	10.4		
Patients treated with serum only	18	6.7		
Patients treated with sulfonamide compounds and serum	38	7.9		
Total patients not treated with serum	27		7	26
Total patients treated with serum	70		3	4.3

means of spinal puncture or the classic signs and symptoms of the disease received serum treatment, and there was no selection of patients.

The results of treatment with serum appeared to be strikingly favorable, especially when treatment was started early in the course of the disease. The effect was even more marked in relief of such symptoms as the distressing

headache (such relief often occurring in a few hours), as well as relief of nausea and vomiting, than the effect on the duration of fever (table 1) and the temperature curves would indicate (figures 3, 4, 5 and 6). Not infrequently headache completely subsided overnight, whereas the signs of the disease, such as rigid neck, still persisted.

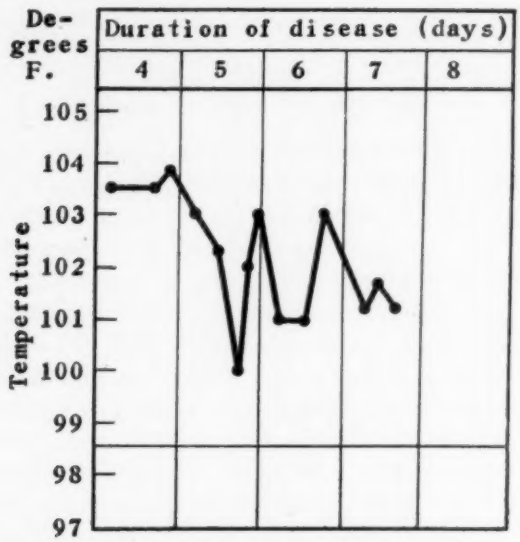

FIG. 3. Temperature curve, patient in case 1.

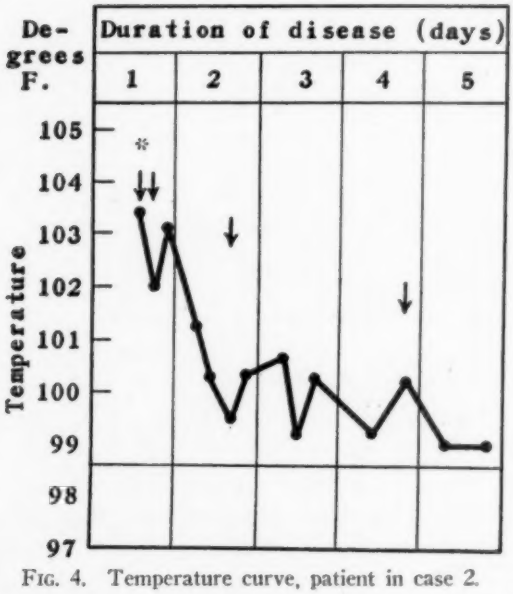

FIG. 4. Temperature curve, patient in case 2.

* The arrows indicate the time of injection of 17, 10, 10 and 5 c.c. of the antistreptococcus serum, respectively.

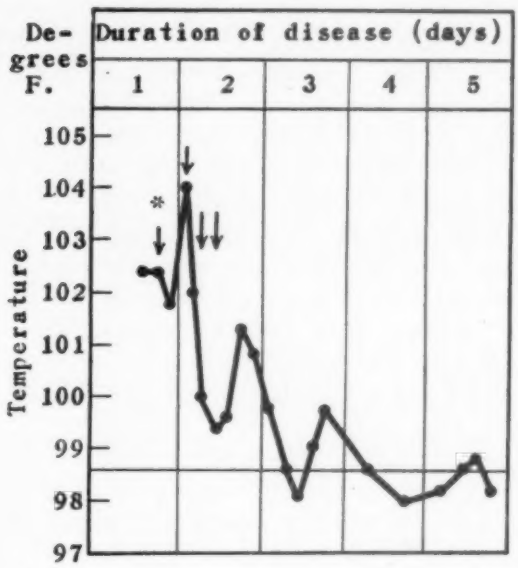

FIG. 5. Temperature curve, patient in case 3.

* The arrows indicate the time of injection of 10, 10, 5 and 15 c.c. of the antistreptococcus serum, respectively.

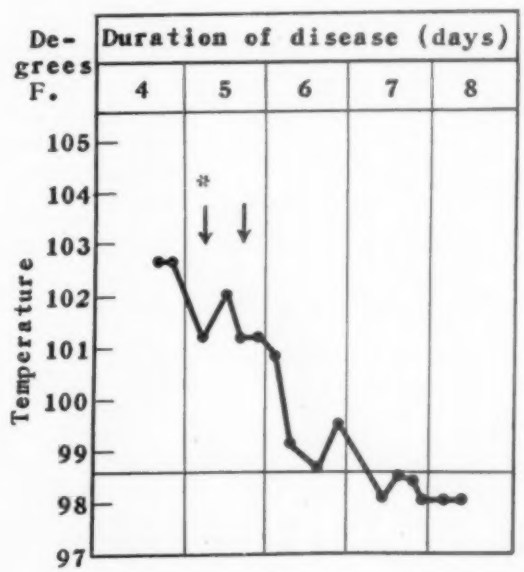

FIG. 6. Temperature curve, patient in case 4.

* The arrows indicate the time of injection of 10 and 10 c.c. of the antistreptococcus serum, respectively.

The dosage of the serum was changed in the latter part of the epidemic, and the change resulted in what was felt to be a more favorable response. Patients treated earlier in the epidemic received 10 or 20 c.c. by intramuscular injection once or twice daily. Later, because of the frequency with which reactions to cutaneous tests returned to positive, the dosage was changed to 5 c.c. injected intramuscularly at four-hour intervals. A secondary increase in temperature was prevented in this manner. We noted not infrequently that when treatment with serum was discontinued, a secondary increase in temperature appeared, and for this reason we recommend that the treatment with serum be continued for at least one day after the temperature has returned to normal. No untoward reactions followed the use of the serum, except for an occasional temporary increase in temperature as an immediate reaction. Hives developed among most of the patients as a late reaction to the horse serum.

The antistreptococcic serum was produced in horses by the injection of streptococci that had been isolated during studies of encephalitis; the antigenic specificity of the streptococci was maintained throughout the long period of immunization.[10]

The following cases have been chosen to typify the extremes in age groups attacked, as well as to emphasize the value of serum therapy when it is administered early, and also to present the variations in symptomatology and laboratory observations among patients ill with encephalitis.

Case Reports

Case 1 (*figure 3*). A 48-year-old farmer was admitted to the Jamestown Hospital complaining chiefly of severe headache, more severe than and unlike any he had experienced in the past. Associated with the headache were persistent nausea and occasional vomiting. These symptoms had been present for four days.

Examination revealed an acutely ill man whose face was flushed, whose conjunctivae were injected, whose throat was diffusely red and whose neck was rigid. Spinal puncture on admission of the patient and examination of the cerebrospinal fluid revealed 37 cells with 15 per cent polymorphonuclear leukocytes per cubic millimeter. Two days later spinal puncture and examination of the spinal fluid revealed 205 cells per cubic millimeter.

The patient's course in the hospital declined progressively. He became irrational and comatose and died on the seventh day of his illness. No serum was given.

Necropsy was carried out by Dr. E. J. Larson, and the brain was sent to the Department of Pathology of the University of North Dakota, where the following report was made: "The entire brain shows marked congestion of the meningeal vessels, especially in the parietal region and over the cerebellum. Some arachnoid roughening along the longitudinal sulcus. Microscopic: marked congestion of the vessels, perivascular infiltration of lymphocytes, plasma cells and few polymorphonuclear cells in the brain stem and cerebrum."

Case 2 (*figure 4*). A farmer 61 years of age was admitted to the Jamestown Hospital on Dr. G. H. Holt's service. This patient had become ill while he was working on a wheat binder. He came to Jamestown and was there found unconscious on the street by friends who brought him to the hospital. After regaining consciousness he complained chiefly of an inability to walk straight or, as he remarked,

"I can't track right." The patient also complained of severe headache and nausea which also had begun on the day of his admission.

Examination revealed a very ataxic, well-developed and well-nourished man with a temperature of 103.4° F. (39.6° C.). His face was flushed and the mucous membrane of the conjunctivae and soft palate was severely injected. Results of neurologic examination, except for hypoactive knee jerks and a rigid neck, were negative.

Examination of the cerebrospinal fluid revealed 160 cells per cubic millimeter and diplococci in the stained sediment.

This patient received about 30 c.c. of serum in two injections and on the next morning was able to walk so much better and his headache was so greatly relieved that he thought himself well enough to return to his work. He was kept in the hospital, however, until he had completely recovered, after he had received a total of 42 c.c. of serum.

This case well exemplifies the value of the administration of the serum early in the treatment of encephalitis. Reactions to cutaneous tests were positive for encephalitis on the day of the patient's admission and were negative the next morning after the patient had received serum.

Case 3 (*figure 5*). A 74 year old man was admitted to the Trinity Hospital on Dr. F. O. Woodward's service. He complained of severe headache and fever with chills of six hours' duration.

Examination revealed the classic signs of encephalitis: temperature 102.4° F. (39.1° C.), moderately stiff neck, and congestion of the face and mucous membranes of the eyes and soft palate. Five lymphocytes per cubic millimeter were found in the cerebrospinal fluid and the blood leukocyte count was 8,000 cells per cubic millimeter.

The headache and other symptoms disappeared overnight, after four injections of the serum, and the temperature receded rapidly to normal.

This case also demonstrates the value of early treatment with the serum of patients ill with encephalitis.

Case 4 (*figure 6*). An eight year old child was brought to the Trinity Hospital, complaining of headache with nausea and vomiting of four days' duration. Dr. E. J. Larson examined the child and made the diagnosis of encephalitis. The reaction to the cutaneous test was positive. Sixty-five cells per cubic millimeter were found in the cerebrospinal fluid. Stained smears of the cerebrospinal fluid revealed diplococci. The leukocyte count was 11,500 cells per cubic millimeter. The symptoms rapidly subsided and the temperature receded to normal within 24 hours after two intramuscular injections of the serum.

Case 5. A woman 23 years of age was admitted to the Trinity Hospital on Dr. Holt's service, complaining of generalized headache unrelieved by acetylsalicylic acid (aspirin). There was no complaint of nausea or vomiting.

Examination revealed a moderately ill woman, whose temperature was 103.4° F. (39.6° C.). Results of the general examination were normal, except for definite injection of the nasopharynx and stiff neck, and those of neurologic examination were normal. The reaction to the cutaneous test was positive. The leukocyte count was 11,500 cells per cubic millimeter. Seventy-two polymorphonuclear cells were found in the cerebrospinal fluid. Examination of the stained smear failed to demonstrate diplococci.

Serum therapy was started at once and on the third day the patient was able to leave the hospital, after having received a total of 40 c.c. of the serum.

Case 6. A farmer 63 years of age became suddenly ill with rightsided hemiplegia one week before his admission to the hospital on July 24, 1941. Apparently he had been perfectly well before the onset of this illness.

Results of the examination, aside from hemiplegia and rigid neck, were normal. The temperature was 102° F. (38.8° C.). Encephalitis was suspected and spinal puncture revealed 400 cells per cubic millimeter of spinal fluid, of which 15 per cent were polymorphonuclear leukocytes. A stained smear of the sediment of the spinal fluid revealed a few cocci. The urine was normal and the leukocyte count was 17,200.

The encephalitis antistreptococcic serum was not available at this time and the patient died the next morning.

Necropsy was performed by Dr. E. J. Larson and the pathologic report from the University of North Dakota follows:

"There is marked congestion of the meningeal vessels, with petechial hemorrhages in the medulla and base.

"Microscopic: Brain stem, midbrain and cerebrum. Congestion of the vessels, perivascular lymphocytes and polynuclear infiltration, perivascular hemorrhages and petechial hemorrhages.

"Diagnosis—encephalitis."

This case is of interest in that organisms were found in the spinal fluid of this patient proved to have had encephalitis. The patient was not seen by either of us.

In addition to the striking clinical improvement which followed injection of the serum, there was a shortened average duration of fever from 10.9 days to 7.2 days (table 1), a prompt recession in temperature, especially when the serum was administered in the early stages of the disease (figures 3 to 6), and a sixfold lowering of the mortality rate among members of the serum-treated group (4.3 per cent) over the rate among members of the control group (26 per cent, as seen in table 1). These results are favorably comparable to the specific serum treatment of pneumonia and to results reported previously in the serum treatment of encephalitis.[11, 12]

In order to guard, in so far as possible, against recurrence and development of the so-called sequelae among persons recovering from this disease, sequelae which our studies have shown to be associated with the effects of neurotropic types of streptococci, it is suggested that all patients receive a series of injections of a detoxified vaccine prepared from strains of the streptococci freshly isolated during this epidemic. This vaccine and the antiserum are available for study.*

Conclusions

On the basis of our studies we are forced to the conclusion that encephalitis is caused primarily by a specific type of streptococcic infection, that the virus is related synergistically or phasally to the streptococcus isolated, and that the serum of horses immunized with this streptococcus is curative.

* Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.

The presence of this particular type of streptococcus among persons and animals ill with this disease, and in well "contacts" and "noncontacts," and its wide prevalence in nature, including the outdoor air in the epidemic zone, are believed to be of great epidemiologic importance, and indicate that the disease may be air-borne.

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PSYCHOLOGIC ASPECTS OF HEART DISEASE*

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A review of the literature on heart disease in which psychologic factors are discussed constitutes an interesting experiment for the internist as well as for the psychiatrist, for not only is the internist likely to be bewildered by the psychiatric terminology and interpretations, but the psychiatrist feels equally confused on reading the papers in the field of internal medicine.

Articles by Paul White,[1, 2] Reid,[3] Hirschboeck,[4] Edwards and White,[5] and Friedlander and Levine [6] stress the sharp differentiation between organic heart disease and so-called "cardiac neurosis." This is also the chief point made by Boas,[7] Willius,[8] and Jukes.[9] Emphasis is placed by several writers on the importance of diagnosing the neurosis by exclusion of organic disease, whereas in no instance with the above is a psychologic disease assigned a major rôle in the etiology of coronary occlusion or the syndrome of angina pectoris.

Turning to the writings of psychiatrists and neurophysiologists there should be little surprise to find that an attempt has been made to show a true relationship between psychic phenomena and certain types of heart symptoms, and that the nature of the rôle of psychic phenomena in the causation of organic heart disease is the subject of considerable psychiatric research at the present time. William Menninger [10, 11] has reviewed the literature and offered a method of classification which we shall not give here. He emphasized the importance of the psychiatric point of view in the study of organic diseases of the heart. Menninger suggested the following as possible steps in the production of some forms of heart disease: first, an emotional disorder causing functional heart disorder, the disturbance continuing for a protracted period of time; second, the continued functional disorder giving rise to structural changes in the form of organic heart disease. Yaskin [12] strongly maintained the inadvisability of using psychic and somatic complaints as criteria for diagnosis. He emphasized the fact that the sympathetic nervous system is subject to emotional factors which affect the heart both directly and also indirectly through alteration of the epinephrine content of the blood, which in turn acts on the heart. Soma Wiess,[13] writing in 1932, discussed the effect of the so-called "emotional storms" on blood pressure and the peripheral vascular bed. Wolfe,[14] in 1934, wrote of the intense repression with anxiety found in patients with "cardiac neurosis." Katzenelbogen,[15] in writing of somatic disorders of functional origin, pointed to the frequency of autopsies of patients who had coronary sclerosis without symptoms and also of those who had typical angina pectoris without coronary disease or disease of the sympathetic nervous system. Although he did not so state he strongly

* Received for publication November 11, 1939.

implied that psychologic factors often play a major and deciding rôle in the production of angina pectoris. Conner [16] mentioned the important rôle of profound grief and prolonged anxiety as a cause of certain cardiac disorders. Kerr, Gliebe and Dalton [17] described the physical phenomena found in anxiety states. These authors spoke of a "hyperventilation syndrome." The chain of circumstances in this syndrome, according to them, was as follows: the individual is faced with a problem to meet; he may face it squarely or attempt to ignore it. If an attempt is made to ignore it, it is the suppressed emotion associated with the conflict that directly stimulates the sympathetic nervous system. This stimulation occurs through the centers of the sympathetic nervous system in the cerebral cortex and the basal nuclei, reaching the heart in the rich plexus of sympathetic fibers arising both from the cervical ganglia and the upper five thoracic nerves. Stimulation of the adrenal glands also occurs, which in turn probably stimulates the heart. There is increase in respiratory rate and in ventilation, with carbon dioxide expelled from the blood stream and the tissues to the alveolar spaces. There is retention of chlorides and phosphates in the blood, with alkalosis, and a resultant irritability of muscle tissue. Others have attributed the symptoms to a constriction of the coronary vessels supplying the heart with blood, due to overstimulation of the sympathetic innervation of the heart, with a resultant asphyxia and myocardial damage. Most authors emphasize the importance of careful psychiatric study of the patient, with relief from conflict as the primary immediate therapeutic goal. Houston [18] pointed out that the term "cardiac neurosis" indicated a profound learned reaction of the heart and its blood supply, which he termed a "spasmogenic aptitude." He suggested that the response of some individuals to early fears and "unpleasant efforts" produced a conditioned response to similar stimuli.

H. B. Day,[19] writing on the "emotional causes of somatic disease," stated that he believed that the physiological effects of emotion may, under certain circumstances, become habitual and result in pathological structural change. Deschamps [20] and Brosse [21] mentioned changes in the electrocardiogram which ordinarily would be interpreted as evidence of organic heart disease, produced, however, by intense concentration of attention as practiced by the Yogis in India. Delius [22] urged the use of the electrocardiogram to detect the transition between functional and organic heart disease. He stated that there was a relationship between subjective pain and changes of rhythm. He stated that many cases during the war diagnosed as "neurotic" might have been found to be organic with electrocardiographic examination. He suggested use of the term "functional cardiac disorder" rather than neurosis in early cases, thereby recognizing the possibility of later structural change.

Dunbar [23] reported three cases with results of therapy at the psychologic level. She pointed out the growing tendency and need to give up our attempt to differentiate sharply functional and organic heart disease. This author also stressed that it is now possible to learn enough about a patient

so that psychic components in illness can be shown in casual sequences to allow diagnoses to be made at the psychologic level, rather than by exclusion of organic disease. Dr. Dunbar reported three cases all helped through psychotherapy, by allowing the psychologic processes to come into conscious relationship with the symptoms. Family history of heart disease as a predisposing factor also seemed important and was present in the cases quoted. She strongly hinted that psychic and emotional factors played an important etiologic rôle and often hastened the development of invalidism and death.

Two cases are here reported, both having been studied from the psychiatric standpoint to a limited degree. The cases are reported because of the rather close relationship between the symptomatology and the psychologic background. In both cases there is history of long-standing so-called psychologic maladjustment, with symptoms which seem closely related and blend into a final "organic picture." Physical examinations and electrocardiographic findings point in both cases to the existence of organic change in the heart. If a long history of psychologic maladjustment, with the production of "tension," is capable of producing first a change in the function of the coronary vessels and later a change in the structure of the vessels, it is possible that one of the types of psychologic processes involved is illustrated in these cases. They are further reported because of their rather remarkable response to treatment at the psychologic level so far as relief of symptoms is concerned.

Case Reports

Case 1. E. S., aged 45, married, was referred to us March 17, 1937. His chief complaint was "heart trouble and crying spells." Family history revealed that the father died at 62 of "acute indigestion and heart failure." The patient was well until June 8, 1936, when he was seized with severe "pain over the heart" with a smothering sensation, a sense of pressure in the chest, and pain down the left arm. These symptoms were associated with a feeling of impending death and marked fear. The attack passed away in a few hours with morphine and rest. Two days later a second and more severe attack of a similar nature occurred and a diagnosis of coronary thrombosis was made by the attending physician. The patient remained in bed for a period of about eight weeks, during which time an electrocardiogram was done (figure 1). In this period of bed rest there were attacks of crying, depression, irritability and restlessness, with pain over the heart. The crying seemed to be without motivation, and suicidal thoughts came to him. There then followed a period at home during which he was mildly active physically. He was irritable toward his wife, was depressed, and suffered with pain over the heart and crying spells. In February 1937, he visited his brother in California, remaining there one month. For the first 10 days of the visit he was moderately free of symptoms and experienced a lessening of tension and a feeling of hopefulness. The pain returned during the second week of his stay, and he consulted a cardiologist who advised him to consult a psychiatrist on his return home. He was referred for examination and treatment March 17, 1937.

At the first interview the patient seemed cheerful on entering the office, but as soon as the door was closed he broke into convulsive sobbing which lasted for nearly an hour. He was occasionally able to intersperse his crying with statements of his hopeless financial situation and profound depression. He was seen regularly thereafter

over a period of two or three months; there was steady improvement of symptoms with complete cessation of them by June 1937. Most of the material discussed in the early interviews had to do with his progressively developing financial failure during the preceding two or three years. This had meant evading more and more those to whom he was indebted so that in the few months before the acute onset of his symptoms he had experienced intense remorse on looking over debts, especially those debts to personal friends. He had been avoiding his creditors on the street and was urged systematically to interview them and explain his financial status. For the most part, however, he was urged to talk freely and as he pleased in the interviews. It is interesting that he reported relief within a week from the acute pain, smothering sensation, crying and depression, and had returned to work with plans for the future. Within this period, furthermore, he could use his visits more calmly to discuss the earlier parts of his life. How much his financial problems entered into his illness as a precipitating factor is illustrated by the fact that he had developed a dread of looking over his debts because of the agitation that act produced. The acute onset, furthermore, came while he was so engaged.

Psychiatric study over the subsequent two or three months revealed a long history of marked inferiority reactions during childhood and adolescence in the form of shyness, evasion of athletic competition, sensitiveness, masturbation with its attendant feelings of guilt, and the development of a proud haughty manner. He recalled witnessing arguments between his father and mother as early as the age of four, at which time pain over the heart with a sense of smothering occurred. He recalled at the age of nine phantasies of killing his father after such arguments. He reported two dreams of his mother being abandoned and being in need of him. He admitted that his wife was not the one with whom he was originally in love and recognized a greater need for his mother than for his wife. There was a period of self-inflicted isolation through adolescence to keep him away from "tough gangs" in his neighborhood, his fear of them being associated with "pain over the heart." The childhood masturbation continued into early adult life until his marriage. He reported intense feeling of guilt, with depression, lasting a day or two on several occasions following masturbation; this feeling of depression was accompanied by pain over the heart and down the left arm and a smothering sensation in the chest. The memories of the above combination of symptoms were clear to the patient, and care was exercised by the examiner not to suggest their presence.

He returned to work during the first week of treatment and after three weeks was working steadily full time. He has since remained continuously at work. Only with the nearly fatal illness of his older son did he experience pain in the region of the heart. Financially he was unable to have more than limited treatment and certainly not long psychiatric study. A total of 15 one hour visits was made, most of them within the first two months. In that time sufficient material was brought into relationship with consciousness to allow him to make a fairly good adjustment. He is cheerful, free of pain, and working steadily. Electrocardiographic studies are shown (see figures 1, 2 and 3), all of them with evidence of myocardial damage and interpreted as probably indicating a previous cardiac infarction. Clinical examinations supported these findings.

Although psychiatric study is incomplete and does not reveal the entire structure of the neurosis, sufficient information was obtained to indicate a psychologic process centered in the Oedipus situation with considerable persistent need for the mother and hostility toward the father. Marked inferiority reactions have continued from childhood to the present time with repression of attendant feelings of guilt. Cardiac pain, suffocation, fear and depression are traceable to the age of four. Attempts at compensation have produced a proud, haughty "extravert" type of behavior maintained for long periods of time, breaking down under stresses such as economic failure,

critical illness in the family, etc. There is laboratory and clinical evidence of organic heart involvement with relief obtained at the psychologic level.

Case 2. C. R. M., 45, married, was first seen June 27, 1939. At the time of the first examination his complaints were that he was depressed, had little interest in work and had feelings of fear, insecurity and of being different from other people. He also complained of pain and a smothering sensation in the chest. The pain passed into the left arm. He stated that the above group of symptoms always occurred when his

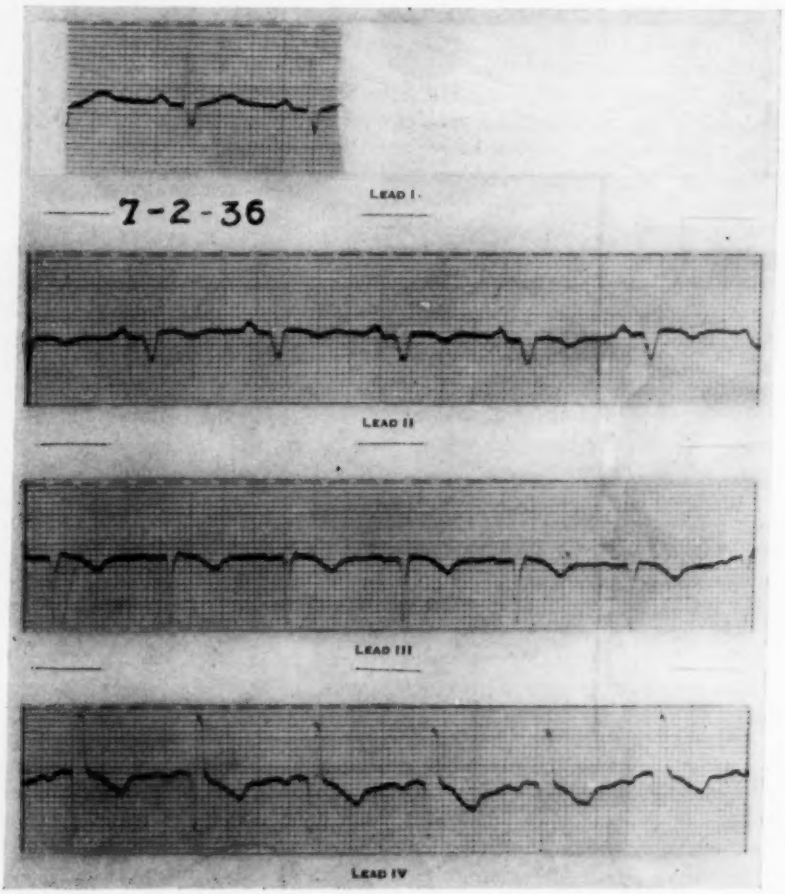

FIG. 1. *Case 1.* EKG, 7–2–36. Rhythm regular. Rate 60. T-waves sharply inverted, Leads II and III. Upright Lead I. Inverted Lead III. QRS: Left axis deviation, slight aberration. Conclusions: T-wave changes suggestive of previous posterior cardiac infarction.

wife was visiting out of town, leaving him at home alone. She was then out of town. At this interview the patient told the examiner that he would not need care over an extended period of time because his wife would soon return from her visit and he expected his symptoms to disappear at that time. He volunteered the information that these same symptoms came whenever he was left at home for more than a day, but that he had been ashamed to ask a doctor about his fear and depression because he felt that he must be a "coward" to be afraid. Until this time, therefore, he had complained to his doctor only about the smothering sensation and the pain in the arm and chest.

He was seen twice within a few days and related the following history. He was born in Iowa. His father and mother had quarrelled violently from the period of his earliest memories. They separated when he was 15, at which time he was left to shift for himself. He recalled being greatly upset during these disputes and experiencing feelings of rage, fear, depression and a smothering sensation in the chest. He described this as a "tightening" that would last for a day or two after the quarrel had subsided. Fear of being alone was present as early as the age of 10. He associated

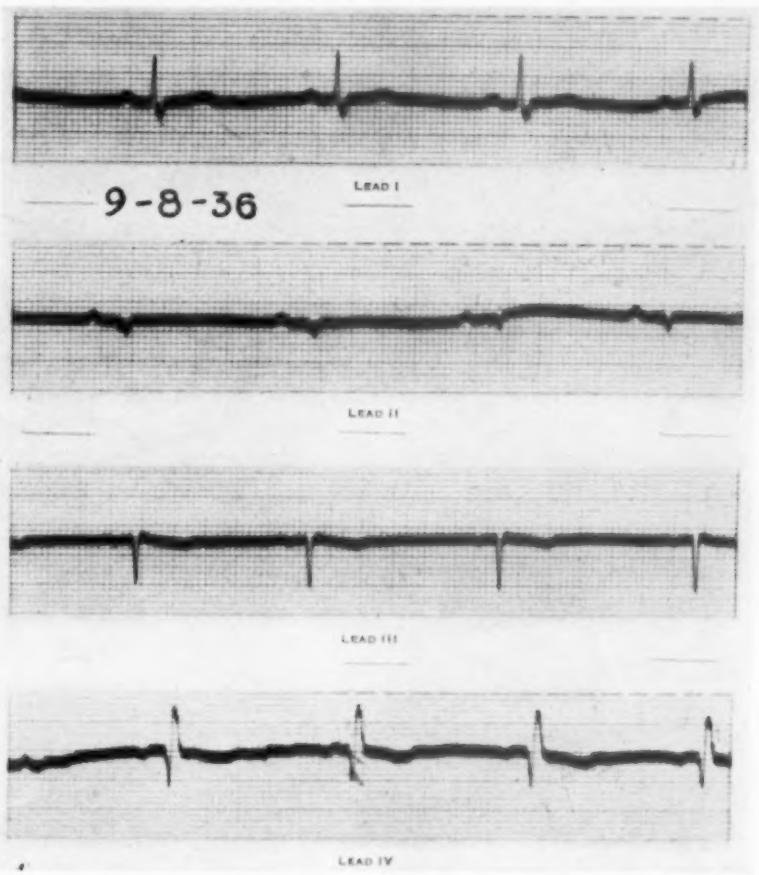

FIG. 2. *Case 1.* EKG, 9–8–36. Since tracing 7–2–36 III is less inverted. T_2 is now flat. T_4 is now flattened. Conclusions: Changes suggest healing posterior cardiac infarction.

the rage and anger with his feeling toward his father during the arguments. He was left alone when 15, and there then followed years of hard work, lonely wandering and poverty in a battle for economic security that had been uphill until recently. From time to time until his marriage he experienced short periods of a day or two of depression, fear of something impending and smothering in the chest. His marriage brought him his first feeling of being wanted by someone. He could recall no similar feeling while living with his parents. Since his marriage he had been free of symptoms, except when his wife was visiting out of town. During her absence depression,

fear, loneliness and a tightening, smothering feeling in the chest were present. Beginning three years previously the above symptoms included pain over the heart. This pain varied from a dull ache to a severe piercing pain which passed into the left arm. He consulted a physician at the onset of the pain and an electrocardiogram was done (figure 4). A diagnosis was made then of coronary artery occlusion. He reported being free of pain and of his other symptoms, except during the occasional absences of his wife.

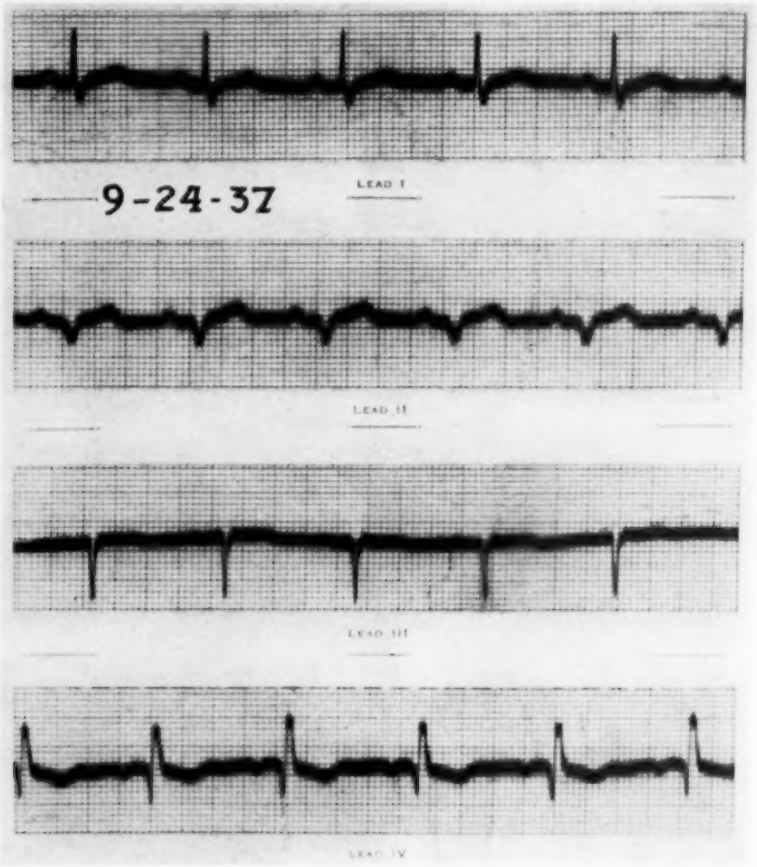

FIG. 3. *Case 1.* EKG, 9–24–37. Rate 66. Rhythm regular. T_2 now upright. T_3 diphasic. QRS: Slight aberration. Conclusions: Changes suggest healing or healed posterior cardiac infarction.

Therapy consisted only in assuring him that his fear and anxiety probably were related to earlier fears of being abandoned and that he showed no evidence of being a coward. The patient reported by telephone on August 25, 1939, that he had not returned for treatment because he had felt well since his last visit and inasmuch as his wife had returned from her trip a few days later he had remained well.

Although more complete psychiatric study was not possible, the patient was convinced of a close relationship between his childhood experiences and his present condition. This much seems evident: that deep resentment existed toward his father, that

his childhood afforded him little love and security, and that at an early age he was forced into adult reality situations without sufficient preparation. In his own opinion his wife fulfills the obligations both of wife and mother to him. It seems reasonable, therefore, to assume that his symptoms represent his childhood and lifelong reaction to abandonment.

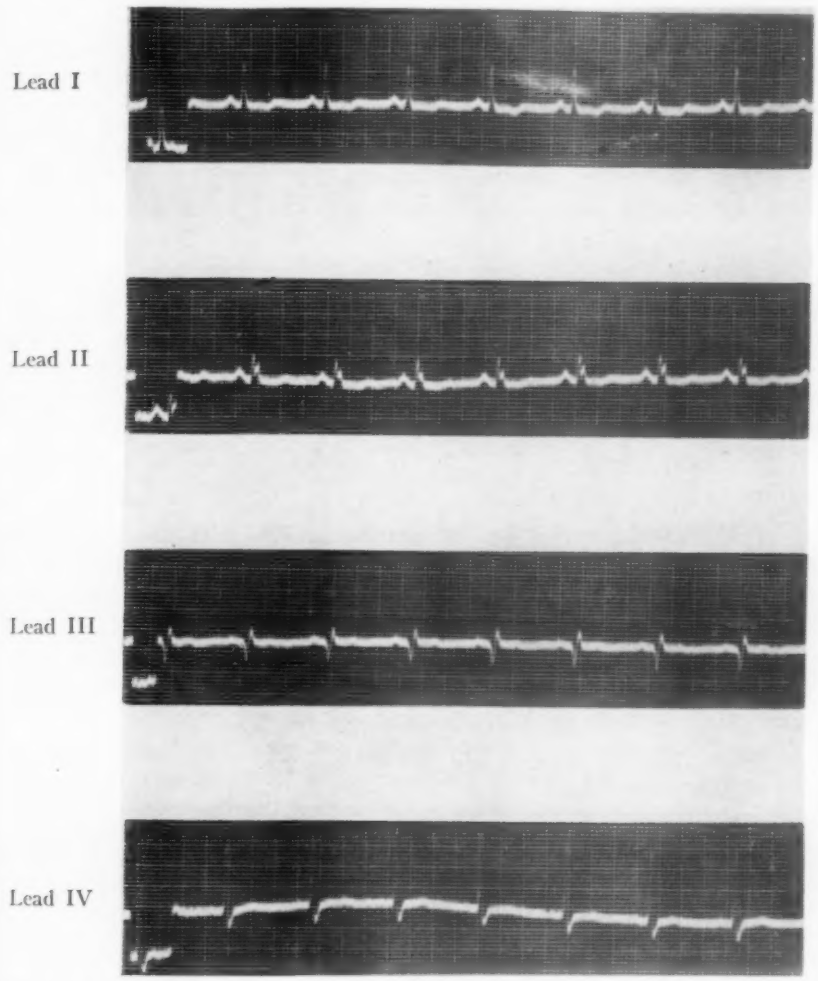

FIG. 4. *Case 2.* EKG, 2-25-39. Sinus rhythm 75. QRS slurred in all four leads. QRS duration .08 second. T_1 is diphasic. T_2 and T_3 are inverted. Q_3 is of 4 mm. amplitude. Conclusions: These findings indicate myocardial damage, probably a result of coronary vascular disease, and suggest the possibility of posterior cardiac infarction.

DISCUSSION

In both cases there is a history of long-standing symptom complexes which follow a pattern rather accurately from early life to the present. Somatic symptoms of pain in the chest and down the left arm, together with

a smothering feeling in the chest, were present in Case 1 from the age of four. In Case 2 pain over the heart did not occur until the age of 42; however, smothering and a "tight" feeling in the chest, fear, loneliness and depression came during and following quarrels between the parents, at which times he also felt rage toward the father. The patient gave the age of eight as the approximate time when the symptoms first appeared. The threatened dissolution of the home seemed sufficient to precipitate the symptom complex. When pain over the heart and in the left arm joined the syndrome many years later, being alone, even though there was no threat of being abandoned, brought on the symptoms. The probable structure of the neurosis in each patient was based on the Oedipus situation with repressed rage against the father and longing and need for the mother. The quarreling of the parents seemed in each case to be a threat of abandonment, actually occurring in Case 2 and nearly so in Case 1. Heart pain, smothering sensations, fear and crying were recalled by the first patient, associated with the quarreling between the parents and carried into fantasies of abandonment by them. Thoughts of killing the father were present in Case 1, and in Case 2 there was intense anger toward the father. In Case 2 attacks were always precipitated by absence of the wife from home for more than a day.

Electrocardiographic examination in each case showed coronary disease. No definite conclusions can be drawn as to the interrelationship between the neuroses present and the cardiac disease. Both neurosis and cardiac infarction can be diagnosed to the satisfaction of both internist and psychiatrist in each case. Treatment at the purely somatic level failed to give relief in Case 1. Rest in bed aggravated the symptoms, and relief occurred only by bringing some of the conflict into relationship with consciousness. This type of therapy produced relief from both "somatic" and "psychologic" symptoms.

It is suggested that psychologic conflict of the above discussed type may create a flow of nervous energy to the vasoconstrictor mechanism of the coronary vascular bed over a long period of time and greater in volume than is found in individuals without such conflict. That secondary changes of an organic nature may take place in these vessels must be considered. Such a process is, however, difficult to prove.

Summary

The case histories of two patients, each with a neurosis dating from childhood and associated later with coronary disease and cardiac infarction, are presented. The structure of the neurosis in each case centered about the Oedipus situation. Treatment at the psychologic level gave relief. Coronary disease is prominent among those whose psychosomatic relationships require further study. The above cases are offered as examples of one type of neurotic conflict which may be involved. It is felt that terminology should be freed of terms sharply delimiting the organic from the psychologic.

Study of "cardiac" patients at the psychologic level should prove fruitful, both for greater knowledge of psychosomatic relationships and for the more intelligent treatment of the patient.

The author wishes to thank Drs. Robert King and Austin Friend for interpretations of electrocardiograms and various suggestions as to terminology.

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SPONTANEOUS HEMOPNEUMOTHORAX: REPORT OF THREE CASES AND REVIEW OF LITERATURE *

By Homer C. Hartzell, M.D., *Cleveland, Ohio*

Introduction

Spontaneous idiopathic hemopneumothorax is an unusual clinical condition which develops when bleeding occurs into the pleural cavity during the course of a spontaneous pneumothorax.

Three patients presenting this condition have been observed at Cleveland City Hospital during the last 10 years. The first two were observed on the medical wards within the last two years. The third was discovered as the result of a survey of cases of pneumothorax and of hemothorax observed at City Hospital during the years 1930–1940, excluding those cases in which active tuberculosis was known to be present.

Case Reports

Case 1. The first patient was a 26 year old machinist who had no history of previous serious illness. One week prior to admission to the hospital he was seized, upon arising from bed, with a sharp stabbing pain in the left chest which radiated to the left shoulder and then gradually spread to the right chest. He attempted to work but was forced to return home after two hours. The following morning while walking to the bathroom the patient fainted. On recovering consciousness he had a profuse sweat, and his family noticed that he seemed unusually pale. The pain in the chest subsided within two days, but he developed progressive weakness, dyspnea on exertion, and low grade fever. He also had a cough occasionally productive of small amounts of yellow sputum. Slight blood streaking had occurred on one occasion.

On admission the patient did not appear acutely ill, but his temperature was 38.2° C., he was dyspneic and appeared pale. Significant physical findings were confined to the chest. A respiratory lag and abnormal fullness of the interspaces were noted on the left. There were dullness, diminished tactile fremitus, and absent breath sounds below the level of the fifth interspace anteriorly and the third interspace posteriorly. Above this area the percussion note was tympanitic, and a few moist râles were heard at the left apex. The heart was displaced to the right. Diagnostic aspiration revealed the presence of gross blood in the left pleural cavity. The red count on admission was 3,090,000, hemoglobin 55 per cent, and white count 13,500. Bleeding and clotting times and the capillary resistance test gave results within normal limits.

A diagnosis of left hemopneumothorax was made.

A roentgenogram of the chest taken on the day of admission showed a dense shadow occupying the lower half of the left lung field, with a fluid level overlying the fourth rib anteriorly. Above this level a pneumothorax was present. Four days following admission, fluoroscopy revealed that the fluid had risen to the level of the clavicle. The patient at this time was moderately dyspneic, but the mediastinal displacement was not sufficient to cause circulatory embarrassment. Therapeutic aspiration yielded 1400 c.c. of blood with a red cell count of 2,800,000. Four hundred cubic

* Received for publication September 25, 1941.

centimeters of air were introduced. Following this aspiration, the fluid was still at the level of the eighth rib posteriorly. The fluid was negative for pyogenic organisms, tubercle bacilli, and tumor cells. Sputum examination was likewise negative for tubercle bacilli.

A second aspiration done two days after the first yielded 1800 c.c. of fluid with a red cell count of 540,000. Two hundred cubic centimeters of air were injected. The fluid withdrawn failed to coagulate after two hours. A second roentgenogram taken at this time showed only a small amount of fluid at the left base. There was still a 50 per cent collapse of the left lung, and no evidence of parenchymal infiltration was present.

At a third therapeutic aspiration seven days after the first, 900 c.c. of slightly bloody fluid were removed. A chest roentgenogram at this time showed a small amount of fluid in the left costophrenic sinus and a residual pneumothorax at the left base. The lung fields were clear. On discharge nine days later, or 19 days after his admission to the hospital, the patient felt well, his temperature was normal, and his red cell count and hemoglobin had risen to 5,470,000 and 14.6 grams respectively.

A roentgenogram taken five weeks following his discharge showed complete reexpansion of the left lung, a clear costophrenic sinus, and normal lung fields. Since this time the patient has worked steadily and has felt well, but he still notices occasional twinges of pain in the left lower chest on deep respiration or during activity involving the musculature of the chest wall.

Case 2. This patient, a 17 year old white boy, was first admitted to Cleveland City Hospital on January 11, 1940, complaining of severe pleuritic pain in the right chest of three days' duration. A roentgenogram of the chest taken the day before admission revealed a pneumothorax on the right side with about 15 per cent collapse of the lung. There was no fluid present, and no emphysematous bullae were seen. The lung fields showed no abnormalities. The pleuritic pain subsided with rest in bed, and the patient was discharged 11 days following admission. A roentgenogram of the chest taken one month later showed that the right lung had completely reëxpanded.

The patient was readmitted on October 18, 1940. Since his discharge he had felt well, but several attacks of "gurgling" in his right chest, associated with mild dyspnea, had occurred, each lasting several days. Three days before admission he developed moderate pain in his lower left chest and mild dyspnea. Both became progressively worse. On admission the patient appeared undernourished and ill. The pain and dyspnea were of moderate severity. His temperature was 37.7° C., pulse 110, respirations 24, and blood pressure 120 mm. Hg systolic and 80 mm. diastolic. The expansion of the left chest was limited. The percussion note was hyperresonant laterally and anteriorly on the left, and dull at the left base. The breath sounds were diminished in the upper left chest and absent at the base. No râles were heard. The heart was displaced slightly to the right. The patient's hemoglobin was 12 grams, red cell count 4,700,000, and white cell count 25,250.

A clinical diagnosis was made of spontaneous pneumothorax with effusion, probably spontaneous hemopneumothorax. This was confirmed by fluoroscopy.

Diagnostic aspiration revealed the presence of gross blood having a red cell count of 3.57 million. A roentgenogram of the chest taken the following morning showed a spontaneous hydropneumothorax on the left with about 25 per cent collapse of the lung. The apex was adherent and the apical pleura thickened. A fluid level was present at the eighth rib posteriorly. The mediastinum was not displaced. Intrapleural pressures varied between minus two and minus 10 centimeters of water.

Subsequent fluoroscopy and examination showed no evidence of further bleeding. Removal of the blood was delayed. Nine days following admission thoracentesis yielded 650 c.c. of blood having a red cell count of 1,000,000. Four days later a second thoracentesis yielded 1000 c.c. of sanguineous fluid having a red cell count of

150,000. Two weeks after admission the lung had entirely reëxpanded, but the left diaphragm was slightly higher than the right, and the left costophrenic sinus was obscured. A roentgenogram one week later showed complete clearing of the left costophrenic sinus. The patient was discharged on November 10, 1940, 23 days following admission.

Case 3. The patient, a 21 year old truck driver, was admitted to Cleveland City Hospital January 4, 1935. For two weeks prior to admission he had a cold and cough, and on one occasion expectorated about one ounce of blood. The night before admission he had a slight pain in his left chest and felt weak and dizzy. On arising from bed at 11 a.m. on the morning of admission, he developed severe pain in his left chest, and a shaking chill. Following this he noticed a hacking cough, and breathing was painful.

His temperature on admission was 38° C. He appeared acutely ill and was breathing rapidly and painfully. Examination revealed splinting of the left side of the chest, dullness to percussion at the left base, with vocal fremitus diminished below the nipple line. An area of tubular breath sounds was present at the upper level of this area in the anterior and posterior axillary lines. The mediastinum was displaced to the right, as indicated by the position of the heart. The red cell count on admission was 3,770,000, hemoglobin 80 per cent and white cell count 19,500.

The clinical diagnosis was spontaneous pneumothorax on the left with an associated effusion.

A roentgenogram of the chest taken three days after admission showed a partial pneumothorax on the left, with a dense shadow having a sharply demarcated upper border occupying the lower two-thirds of the left lung field. The mediastinum was displaced to the right. Thoracentesis was done, and 200 c.c. of gross blood were removed from the left pleural cavity. A tuberculin test done with 1:1000 dilution of old tuberculin was positive.

The patient showed gradual symptomatic improvement, and no attempt was made to remove the large quantity of blood which remained. He was discharged January 22, 1935, 18 days following his admission. A chest film taken two weeks after his discharge showed complete reëxpansion of the left lung, a small amount of fluid still remaining in the left costophrenic sinus, but no evidence of infiltration of the lung fields. There were large calcified nodes present in both hilum regions. Three months later a roentgenogram of the chest showed the left costophrenic sinus to be entirely clear and the lungs to be normal.

The patient was recently examined again, after a lapse of six years. In the interim he had felt well and had worked steadily as a truck driver. A recent chest film showed no evidence of retraction of the left chest or of pleural thickening. The left costophrenic sinus was clear, and there was no evidence of parenchymatous infiltration of the lung fields.

The following discussion concerns only those cases of hemopneumothorax without apparent cause, and consequently excludes those cases following trauma and those associated with recognized active tuberculosis and malignancy, in which a cause for the bleeding is evident. A distinction is also drawn between true extravasation of blood into the pleural space and those conditions wrongly termed hemopneumothorax in which the effusion is merely blood-tinged.

Historical

Two articles appearing together in the Transactions of the Clinical Society of London for 1900 are so complete that little of crucial importance

has been said since. Pitt,[1] the first of the two authors, comments that "hemopneumothorax is an extremely rare lesion; there is no reference to it in the Index-Catalogue of the United States Library, nor is it discussed in any of the standard treatises on medicine in either English, French, or German." He presents the case of a boy 18 years old, in whom the sudden onset of pain in the right shoulder and chest was followed by the development of signs of pneumothorax with effusion on the right side associated with profound shock. Insertion of a Southey tube in the right axilla resulted in the discharge of both blood and air, but despite this treatment the patient died. "At the inspection about eight pints of fluid blood, and enough clot to fill the hands three times, together with a considerable amount of air under great tension, were found to occupy the right pleura. The right lung was tightly compressed, and the left base slightly so posteriorly. The lungs were absolutely healthy, with the exception of a small projecting emphysematous bulla, about half an inch across, near the right apex, the wall of which was imperfect; and attached to this was a fibrous band, of the thickness of a knitting needle, which had been torn across. The blood may have come from a vessel in this adhesion, but no aneurysmal pouch or obviously patent vessel could be seen."

Rolleston [2] presented the chief clinical variant of the condition, namely, hemopneumothorax with abdominal symptoms so severe as to simulate an acute abdominal catastrophe. His patient, a man 21 years old, was suddenly seized with intense pain in the right side of his abdomen, radiating to his right shoulder and to the umbilicus. On admission to the hospital he was in a state of collapse and was considered to have generalized peritonitis following perforation of a duodenal ulcer. Laparotomy was avoided only because death seemed imminent. Two days later the patient was somewhat improved; there were signs of pneumothorax on the right side; and insertion of a trocar revealed the presence of air and blood in the right pleural cavity. The patient died rather suddenly five days later. At autopsy 60 ounces of dark fluid blood together with a few ounces of clotted blood were present in the right pleural cavity. There were no pleural adhesions nor lung disease, nor was a source of bleeding evident. A similar lack of significant autopsy findings is noted by later observers.

Incidence

Spontaneous hemopneumothorax is an uncommon condition. Frey,[3] in a review of the literature in 1935, was able to discover only 13 reported cases. Of these, only 10 were truly spontaneous. The remaining three were associated with recognized tuberculosis, one of the three in association with artificial pneumothorax. Since that time many additional cases have been reported. The largest series published to date is that of Louria,[4] who reported five cases.

In compiling cases reported in the literature, only those reports were included which were examined personally, and only those in which tubercu-

losis could be excluded satisfactorily as the cause of the condition. Within these limits we have discovered reports of 40 cases in the literature, which, with the addition of the three cases observed at Cleveland City Hospital, makes a total of 43 cases.

Examination of these 43 cases reveals a striking constancy in the age and sex incidence of the idiopathic lesion. With the single exception of a case reported by Hopkins,[5] all the patients observed have been men. Unless due to the greater activity of men as compared to women, the explanation for this is obscure.

The age incidence of the lesion is equally constant. The age of the patient is indicated in 41 of the 43 cases. Of these, 36, or all but five, occurred in persons between the ages of 20 and 40 years. Three of the five remaining cases occurred in persons 15 to 20 years old, and the two others in persons between the ages of 40 and 45 years.

The lesion involved the left side of the chest slightly more frequently than the right; 24 of the 43 cases involved the left side, and 19 cases involved the right side. This difference is probably not significant. Of the 14 fatal cases, nine occurred on the right side and five on the left.

Pathogenesis

The present concept of the origin of benign spontaneous pneumothorax is that it results from the rupture of a valve vesicle situated on or near the pleural surface. These vesicles are rarely found in routine autopsies; according to Kjaergaard,[6] they occurred approximately once in 350 autopsies in his material. Their morphology has been studied by Fischer and by Hayashi.[7] They are thin-walled structures which may occur either as a sequel to the cicatrization of healed tuberculosis or as manifestations of localized emphysema. They communicate with neighboring bronchioles by means of a valve-like mechanism which permits the easy entrance of air but hinders its exit. The valve may consist of deformed atrophic lung tissue or may be due to bronchiolar constriction resulting from localized inflammatory processes. Because of this valvular action, the vesicle gradually becomes inflated and dilated and may rupture either as a result of exertion or during the course of normal respiratory movements. Vesicles have been observed at the autopsy table in some fatal cases of spontaneous pneumothorax and have been demonstrated radiologically in the living subject by Gordon [8] and others.

Other explanations of spontaneous pneumothorax are not wanting. Kirshner [9] has asserted that idiopathic pneumothorax may be the result of a congenital pleural defect and that pleural blebs are formed as a manifestation of a primarily weakened pleura. Hamman [10] has observed pneumothorax in two of seven cases of spontaneous mediastinal emphysema and thinks that it is due to rupture through the thin mediastinal wall permitting the escape of air into the pleural cavity. Kirshner, in a later article,[11] advances the

explanation that pneumothorax may be due to the rupture of pleural bullae formed secondary to a localized interstitial subpleural emphysema resulting from the rupture of an alveolus or terminal bronchiole with the escape of air into the interstitial tissues.

Evidences that ruptured bullae are significant in the causation of hemopneumothorax are, first, their frequent occurrence in autopsied cases of hemopneumothorax; second, the roentgenologic demonstration of bullae in non-fatal cases; and third, the successive occurrence of spontaneous pneumothorax and hemopneumothorax in the same patient. The autopsy findings in cases of hemopneumothorax are given below. Undoubted bullae have been demonstrated roentgenologically in at least two cases of spontaneous hemopneumothorax, those of Castex and Mazzei,[12] and of Troisier, Bariéty, and Dugas.[13]

The second of the Cleveland City Hospital cases represents one in which a spontaneous pneumothorax was followed within the year by spontaneous hemopneumothorax on the contralateral side. Rist [14] reported the case of a young Chinese student in whom a spontaneous pneumothorax of the idiopathic variety associated with a small amount of hemorrhagic fluid was followed almost two years later by a spontaneous pneumothorax on the same side. Rossel [15] has described an autopsied case of massive idiopathic hemopneumothorax which was suddenly fatal owing to the development of contralateral pneumothorax five days later. In the case reported by Palmer and Taft,[16] spontaneous pneumothorax was preceded by two years by the development of a contralateral hemothorax of unknown etiology.

Autopsy Findings in 14 Cases of Fatal Hemopneumothorax

The autopsy findings in 14 published cases of fatal hemopneumothorax are as follows:

1. Pitt [1] discovered a ruptured emphysematous bulla at the apex of the involved lung, to which was attached a torn adhesion. He suggested that the bleeding may have come from a vessel in the adhesion. A patent vessel was not seen.

2. Rolleston [2] found no lung disease, pleural adhesions, or source of bleeding.

3. Fischer's case [17] presented bilateral areas of localized emphysema and scarring due to healed pulmonary tuberculosis at both apices. On the side of the hemopneumothorax there was observed a large vesicle covered with coagulated blood, from which fresh blood oozed on pressure.

4. Kiaer's patient,[18] as summarized by Perry,[19] showed no significant pathologic change either in the lung or on the pleural surface.

5. Housden and Piggot's case [20] revealed a small puckered tuberculous scar at the apex of the involved lung, multiple discrete and coalescent emphysematous bullae, and also two torn apical adhesions. No source of

bleeding or site of rupture of the lung was found, but the authors felt that the abnormalities found probably explained both the escape of air and the bleeding.

6. Davidson's first case [21] disclosed contralateral adhesions and a small tuberculous scar. On the side of the hemorrhage, however, no lesions were found, nor was the source of the bleeding identified.

7. In the second case of Davidson [21] delicate vascularized adhesions were present associated with a chronic bronchopneumonia. It was assumed that these were the source of the escaping blood.

8. Rossel's case [15] was one of hemopneumothorax with death due to the development of contralateral pneumothorax five days later. On the side of the bleeding, a pea-sized thick-walled umbilicated bulla was found within an area of tissue induration, but the site of escape of blood and air was not determined. On the contralateral side, a ruptured subpleural bulla was found.

9. Tait and Wakeley [22] report an autopsied case showing, on the side of the bleeding, a series of about 12 bullae in and near the apex, ranging, when distended, up to the size of a small cherry. One of these had perforated, and the aperture was filled with recent blood.

10. Jones and Gilbert [23] found in their case an emphysematous cavity 1 cm. in diameter at the apex of the involved lung, but no communication between this cavity and the pleural space, no adhesions, and no source of bleeding were observed. Organizing fibrin masses were present, which constricted the mediastinum and which were presumed to have caused death from circulatory obstruction.

11. Louria's case [4] showed a ruptured emphysematous bleb in the interlobar sulcus of the homolateral lung, without evidence of a source of bleeding. The contralateral lung showed healed tuberculosis, a few adhesions, and emphysematous blebs.

12. The autopsy on Perry's case [19] revealed on the side of the bleeding fibrous adhesions extending between the upper lobe and the parietal pericardium. Hemorrhagic infiltration was present in these adhesions, but the actual bleeding point was not identified, nor was a perforation of the pleura discovered. Intact bullae, subpleural fibrosis, and other adhesions were also present.

13. Davidson and Simpson [24] discovered a ruptured bulla at the apex of the involved lung. They also observed blood issuing from a small band of adhesions at the corresponding base. There was a small apical tuberculous scar. They concluded that collapse of the lung resulting from rupture of the apical bulla had stretched and torn the adhesions at the base, and that slow but continuous bleeding from these adhesions was responsible for death.

14. Lorge's case [25] showed slight scarring and a few emphysematous bullae at the apex of the involved lung. However, the pleural surface was everywhere intact, and no source of bleeding was found.

In summary, a survey of the autopsied cases of hemopneumothorax reveals that in most instances the source of bleeding is not clearly identified. Torn adhesions and ruptured bullae have been implicated in some of the cases. Mazzei and Pardal [26] have shown that, contrary to the usual conception, subpleural bullae may be richly vascularized. They have demonstrated in the lining of the bullae a layer of new formed vessels with abundant communicating anastomoses, which could well give rise to significant intrapleural hemorrhage. The second possibility is that adhesions torn by the traction of the collapsing lung are responsible for the bleeding. Leopold and Lieberman [27] found adhesions at autopsy in almost 50 per cent of all persons above the age of 20, after eliminating those cases with a history of acute or chronic pulmonary disease. The vascularity of adhesions is well known to the thoracic surgeon, and bleeding from adhesions is the more sinister since their blood supply, according to Matson,[28] is derived largely by collaterals from the intercostal vessels. Bleeding may occur as a result of complete rupture of the adhesion or as a result of a tear at the base of an adhesion still retaining its attachment to the visceral pleura.

To determine whether the hemorrhage in a given case is parietal or pulmonary in origin is nearly impossible. Since adhesions of parietal vascularization carry an arterial pressure which is six times that of the pulmonary circuit, ruptured adhesions seem to explain most satisfactorily the source of massive intrapleural hemorrhage. Moreover, the collapse of the lung should usually stop hemorrhage arising from subpleural bullae, whereas it would exert no hemostatic action on bleeding from torn adhesions. Hemorrhage from intercostal arteries is noted for its severity, but these can be implicated only indirectly in spontaneous intrapleural bleeding.

The duration of time required for the pleural space to fill with blood is also of interest. In most cases of hemopneumothorax which do not prove fatal, the bulk of the bleeding has already occurred when the patient is first seen. Rist and Worms,[29] however, observed a case in which signs of dry pneumothorax were followed 12 hours later by evidence of extravasation of blood. I have seen a massive pleural hemorrhage following a pneumothorax refill develop over night when, 12 hours following the refill, the quantity of blood present as seen fluoroscopically was insignificant. The occurrence of slow but cumulative intrapleural bleeding lends plausibility to the contrast between the massiveness of the extravasation of blood and the apparent insignificance of its source.

Tuberculosis and Occult Causes of Hemopneumothorax

The manifest causes of hemopneumothorax are beyond the scope of this discussion. Hemopneumothorax in tuberculosis usually occurs when the disease is both obvious and advanced. Consequently, cases in which tuberculosis is not obvious or easily discovered at the time of the episode of bleeding may confidently be considered non-tuberculous. Milhorat [30] re-

ported a six and one-half year follow-up of a case of hemopneumothorax. The roentgenogram showed a shallow costophrenic angle on the side of the previous lesion, with pleural thickening and irregular calcification in the lower lateral lung field. It also showed some thickening of the apical pleura, which Milhorat interpreted as indicative of an old apical tuberculous lesion. There was no evidence of active disease.

Two exceptions may be noted to the rule that tuberculosis causing hemopneumothorax is both advanced and obvious. Beatty [31] has reported the case of a colored man 20 years old who at the time of his hemopneumothorax had no infiltration in the homolateral lung and only a small amount of apical infiltration in the contralateral lung. Four months later the patient developed frank cavitating tuberculosis in the contralateral lung, and his sputum was positive for tubercle bacilli. This was treated by pneumothorax with improvement. Birch [32] observed a fatal case of hemopneumothorax in which autopsy disclosed a minute tuberculous cavity at the apex of the involved lung. There was no evidence of tuberculosis elsewhere. The source of escape of blood and air was not certainly identified, but appeared to be a roughened area on the pleural surface, since the cavity wall was intact.

Hemopneumothorax is uncommon even in frank advanced pulmonary tuberculosis. Lung collapse in the presence of advanced pulmonary disease is far more apt to result in pyopneumothorax than in intrapleural bleeding. Heise and Krause [33] reported a fatal case occurring in a man with rapidly progressive caseous tuberculosis, developing after his first pneumothorax treatment. Intrapleural bleeding following pneumothorax refills has been reported, and we have observed two such patients during the past year at Cleveland City Hospital. One of the patients made a complete clinical recovery; the other, some weeks following his episode of intrapleural bleeding, developed a spontaneous collapse of the lung on the same side which resulted in mixed infection empyema. Weiner and Jackson [34] have reported the occurrence of spontaneous bleeding and collapse of a lung under treatment by artificial pneumothorax in a tuberculous patient who had had a thoracoplasty on the contralateral side.

It is at first thought surprising that hemopneumothorax does not occur more often as a complication of manifest pulmonary tuberculosis. Korol [35] provides a partial answer to this question. In the first place, lung perforation involves the periphery of the lung where the blood vessels are small, and tuberculous lung tissue, the seat of the perforation, is characteristically poor in blood supply. In the second place, the collapse of the lung which results from pleural perforation brings about a retraction of the injured blood vessels and mechanically tends to stop bleeding.

Among the occasional occult causes of spontaneous intrapleural bleeding, Jacob [36] has reported a case of spontaneous hemopneumothorax in a young man with a history of hemoptysis and expectoration since childhood. Clinically he was considered to have bronchiectasis, but the diagnosis was not confirmed by bronchograms.

Malignancy involving the pleura gives rise commonly to a bloody effusion, but less frequently to the escape of frank blood. Hemothorax due to malignancy is not accompanied by the escape of air into the pleural space.

The Clinical Picture

The picture of idiopathic hemopneumothorax is that of an acute illness, and the most striking and most constant early symptom is pain. In some cases an initial period dominated by pain is followed by a latent period of apparent improvement, and this is then followed by evidence of shock and collapse resulting from intrapleural bleeding and mediastinal displacement. In occasional cases the onset of the pain is associated with coughing, straining, lifting, or some other exertion altering the intrapleural pressure.

The initial pain is usually sudden in onset, sharp, stabbing, and continuous in character, localized to the side of the chest which is involved. The pain may remain localized, but not uncommonly radiates to the shoulder of the involved side, and, significantly, frequently radiates to the abdomen. Dyspnea in some degree usually appears immediately or after an interval. Nausea, vomiting, and even diarrhea are not uncommon. Shock, anemia, signs of collapse and of internal hemorrhage follow in the more severe cases. The physical findings are those of pneumothorax with effusion, and the chest film is diagnostic of hydropneumothorax. The laboratory findings are not characteristic. An anemia develops which is proportional to the extent of intrapleural bleeding. A moderate leukocytosis is usually present.

Finally, a few helpful diagnostic hints may be mentioned. First, the association of signs of hydropneumothorax with those of anemia and internal hemorrhage, coupled with a clinical history of short duration, permits the diagnosis of hemopneumothorax. Second, an effusion appearing within a few hours in a pneumothorax space either artificial or of spontaneous origin is almost certainly blood, for a serous effusion develops only after a pleural reaction lasting one or several days. Third, excluding tuberculosis, the other causes of massive intrapleural bleeding do not at the same time produce pneumothorax. Thoracentesis will quickly determine the nature of the fluid present. In doubtful cases, it is advisable to do a red cell count on the fluid withdrawn, to make sure that it is largely blood and not merely bloody exudate.

Hemopneumothorax with signs referred to the abdomen constitutes the chief clinical variant of the condition. The combination of right upper quadrant pain, shoulder pain, and nausea and vomiting, with occasionally obliteration of liver dullness, has proved especially confusing. The explanation for the abdominal pain is to be found in the common innervation of the lower parietal and diaphragmatic pleura and the abdominal viscera by sympathetic nerves connecting with the lower six thoracic segments of the cord. Exploratory laparotomy was performed in the case reported by Fischer,[17] and was avoided by Rolleston only because his patient seemed

moribund. Grabfield [37] has reported a case simulating acute appendicitis, and abdominal symptoms were prominent also in the cases reported by Hurxthal [38] and Milhorat.[39] The patient reported by Rist and Worms [29] was first suspected of coronary occlusion.

The State of the Blood in the Pleural Cavity

Aspiration in cases of hemopneumothorax yields dark fluid blood, and at autopsy the majority of the pleural blood is unclotted. The fluidity of the blood has been observed not alone in spontaneous hemopneumothorax, but also in pleural bleeding of traumatic and other origin. According to Sacquepee, blood in the pleural space becomes incoagulable after contact with the pleural membranes for four to five hours in man, after two hours in the dog. This is true only if the pleura is not infected. Consequently, the discovery of clotted blood when performing thoracentesis means either that bleeding has not yet stopped, or that infection has taken place.

The probable explanation of the incoagulability of blood in hemothorax originates with Trousseau. According to this author, blood actually clots rapidly in the pleural cavity, even more rapidly than in external hemorrhage. As a result of agitation produced by cardiac and respiratory movements, the blood is rapidly defibrinated and the fibrin deposited on pleural surfaces before the red cells have had time to precipitate. Massive deposition of fibrin on pleural surfaces and surrounding the mediastinum was observed in the autopsied case of Jones and Gilbert, and these authors attributed the death of their patient to circulatory obstruction resulting from the contraction of organizing fibrin masses. In other autopsied cases, fibrin masses have not been found.

Eosinophilia is frequently observed in the intrapleural blood and its serous diluent during the process of resorption. Eosinophilia in pleural effusions is discussed by Grabfield.[37] The explanation of Klein, that the eosinophiles represent neutrophiles which have engulfed hemoglobin from red cells, appears improbable, in his opinion.

Course and Prognosis

Fourteen of the 43 cases, or approximately one case in three, terminated fatally. This figure doubtless exaggerates the mortality of spontaneous hemopneumothorax, both because authors have been more ready to report autopsied cases and because especial care has been taken to include reports of autopsied cases in this discussion.

Of the 14 fatal cases, satisfactory data are available concerning the time of death of 11 cases. Of these 11, five died within 24 hours of their admission to the hospital, four additional patients died within a week, and in two cases death occurred after more than a week in the hospital. One of the latter two died after 28 days in the hospital, apparently of mediastinal obstruction due to organizing fibrin masses. Earlier deaths are due to shock,

anemia, and respiratory and circulatory embarrassment associated with mediastinal displacement.

The escape of blood into the pleural space evokes an inflammatory response manifested by fever, pleuritic pain, and reactive serous effusion. The serous effusion subsides gradually with repeated tapping. The occurrence of empyema following spontaneous hemopneumothorax is a rarity.

Treatment

The treatment of idiopathic hemopneumothorax is based upon several considerations. In the first place, the pneumothorax and the positive intrapleural pressure are probably beneficial to the extent that they tend to stop bleeding. On the other hand, the mediastinal displacement, a result of the positive intrapleural pressure, is harmful when present to the extent that it embarrasses the circulation and respiration. The physician is, therefore, impelled both to withdraw the blood and to do nothing, and his decision will depend upon the time of the illness at which he sees the patient, the degree of mediastinal displacement, and the probability that the bleeding has stopped. A third consideration which will influence his treatment is the possibility that the blood is obscuring tuberculous infiltration of the lung parenchyma and his desire to maintain the pneumothorax artificially until he can be certain of the integrity of the underlying lung tissue.

If the patient is seen soon after the onset of the illness, only enough blood should be removed for diagnostic purposes, provided the mediastinal displacement is not sufficient to cause distressing dyspnea or to embarrass the circulation. Delayed removal of the blood may then be performed, and air injected sufficient to prevent too sudden an alteration of the intrapleural pressure and to maintain the pneumothorax if it is desired to do so.

Shock when present must be treated. Infusions and transfusions are resorted to with reluctance dictated by the possibility that they may initiate fresh bleeding. Withdrawal of the pleural blood and its re-infusion into the patient's veins has been advocated by Rossi, and practiced by Brown and Debenham [40] in cases of traumatic hemothorax. The procedure is doubtless safe, but seems unnecessary in view of the simplicity of modern transfusion technic.

In the more serious cases improvement fails to occur with these medical measures, and fluoroscopic observation of the level of fluid in the pleural space provides evidence that the bleeding continues. Open operation in an attempt to find the bleeding point may then be considered if a hardy surgeon is available. There is no report of attempted operative treatment of spontaneous hemopneumothorax among the cases which we have compiled.

Summary

Three cases of idiopathic hemopneumothorax have been presented, and the literature has been reviewed briefly. The condition is seen in healthy

young men without a history of previous lung disease. Clinically it presents in rapid sequence the onset of chest pain followed by dyspnea, anemia, and shock associated with mediastinal displacement. Its physical findings are those of hydropneumothorax at times associated with confusing abdominal signs. Its pathogenesis is not entirely clear, but some cases are known to develop when spontaneous pneumothorax resulting from rupture of an apical bulla is complicated by the tearing of pleural adhesions during the course of the collapse of the lung. Treatment consists of rest, thoracentesis with or without the introduction of air, and possibly surgical intervention when necessitated by continued bleeding. The condition has no relation to active tuberculosis, and the prognosis, provided the patient survives the acute episode, is good.

The Cleveland City Hospital Cases are presented through the courtesy of Dr. R. W. Scott, Director of the Department of Medicine of the hospital.

I am grateful to Dr. S. E. Wolpaw for suggestions used in the writing of this paper.

Addendum: Since this paper was submitted for publication, an additional case of spontaneous hemopneumothorax has been seen at Cleveland City Hospital. The patient was a white male 22 years of age, and the right side was involved. Thoracentesis performed two and three weeks after the onset yielded 1000 c.c. of blood and 650 c.c. of bloody fluid respectively. His convalescence was uneventful and roentgenograms of the chest failed to reveal lung disease.

His past history was significant in that it disclosed an episode of chest pain and dyspnea appearing following heavy lifting two years prior to the development of hemopneumothorax, strongly suggestive of the previous occurrence of spontaneous pneumothorax on the homolateral side. He was not studied roentgenologically at that time, and the association of spontaneous pneumothorax and spontaneous hemopneumothorax therefore remains unproved in this case.

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BACTERIAL ENDOCARDITIS AND CONGENITAL HEART DISEASE (WITH REPORT OF TWO CASES) *

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The purpose of this paper is to present two interesting cases of congenital heart disease terminating fatally with the development of bacterial endocarditis. The first case, that of bacterial endocarditis superimposed on a bicuspid aortic valve, illustrates the devastating effects produced by this combination of lesions; the second, that of bacterial endocarditis superimposed on the margins of a ventricular septal defect, presents the exceedingly rare situation of an acquired complete auriculo-ventricular dissociation related to the endocarditis.

Case Reports

Case 1. A 36-year-old white man, prematurely gray, was admitted to the medical service of the Roosevelt Hospital on January 21, 1940, complaining of fever and chills of one week's duration. Past history was essentially negative. He was acutely ill, with a rectal temperature of 104° F. The pharynx appeared reddened. The lungs were clear. The heart was not enlarged; there was regular sinus rhythm. A soft apical systolic murmur was noted. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. The spleen was just palpable under the left costal margin. There were no meningeal signs. No rash was noted. There was a slight leukocytosis, and a slight secondary anemia. Roentgen-rays of the lungs and heart were negative. Three days after admission small macular spots appeared on the skin of the anterior chest. The systolic murmur previously heard became harsher and louder. Conjunctival, palatal and retinal hemorrhages appeared. Because of the development of slight stiffness of the neck and a questionable Kernig sign, a spinal puncture was done. The fluid removed was normal in all respects. The next day a diastolic murmur, best heard in the third left intercostal space, became audible. A blood culture was then reported positive for *Streptococcus viridans*. Eight days after admission the right radial pulse became markedly reduced in volume. This suggested embolic occlusion of this vessel. At this time there appeared painful areas on the fingertips having the characteristics of Osler nodes, petechial hemorrhages over the heads of the metacarpals (palmar surface), and Janeway spots (palms). Several days after the reduction in the volume of the right radial pulse there appeared, just below the bend of the right elbow, a very circumscribed area of pulsation. Several days later the patient developed a right hemiplegia. After this the course was rapidly downward, being characterized by spiking temperature and increasing signs of toxicity and stupor. Just before death a pericardial friction rub was noted. The patient died three weeks after admission. Permission was obtained for autopsy, excluding examination of the cranial contents.

Summary of Autopsy Findings. The pericardial cavity contained about 200 c.c. of turbid, reddish brown, bloody fluid. Its lining was roughened with fibrinous exudate. Hemorrhages studded the anterior surface of the pulmonary conus. The

* Received for publication August 14, 1941.

heart was slightly enlarged, the ventricles considerably dilated. The myocardium was brown and flabby, but free of fibrosis. The posterior wall of the left ventricle over an area measuring 3 by 5 cm. in its entire thickness was necrotic, and gray-green in color. Its midportion was thinned out, measuring 5 mm. in contrast to the wall at the base which was 15 mm. thick. There was no mural thrombosis. The aortic ostium was narrowed by a large vegetation which measured 2 cm. from side to side and 3 cm. from above downward. It was 1 cm. thick (figure 1). Its surface was uneven and

FIG. 1. Heart showing large aortic vegetation, embolus in coronary artery and myocardial infarct.

presented pale green, smooth zones with areas of hemorrhage and fibrin deposit. The valve was deeply ulcerated. The vegetation extended toward the left ventricular chamber to a point close to the attachment of the valve, upward over the valve, and down into the sinus of Valsalva. The part of the vegetation which almost filled the sinus of Valsalva was attached to the endocardium of the latter on either side of an incomplete partition which extended as a ridge from the aortic wall to the valve leaflet. This ridge incompletely divided the sinus of Valsalva into two parts, from each of which a coronary artery arose. The affected leaflet was one component of a bicuspid aortic valve. It measured 4 cm. across. The uninvolved leaflet was thickened and fibrotic and measured 3 cm. About 3 mm. distal to the origin of the right coronary artery its lumen was occluded by an embolus having the same appearance as the vegetation. The remaining valves were normal in appearance. The right radial artery at a point 3 cm. from its origin was occluded by an embolus. Its wall was thinned out and structureless, but no actual aneurysmal dilatation could be made out.

Microscopic Examination. The aortic vegetation was made up of fresh and necrotic fibrin with dense focal accumulations of polymorphonuclear leukocytes. Gram stains revealed gram-positive cocci deep in the substance of the vegetation. The myocardium showed necrosis of muscle fibers and acute myocarditis. No bacteria were noted in the myocardium. The wall of the radial artery was necrotic and infiltrated with polymorphonuclear leukocytes. The pericardium showed beginning organization of an acute fibrinous pericarditis.

Anatomic Diagnosis. Bacterial endocarditis of aortic valve (bicuspid)—*Streptococcus viridans.* Embolic occlusion of right coronary artery with infarction of posterior wall of left ventricle. Embolic occlusion of right radial artery with necrosis of its wall. Hemorrhagic fibrinous pericarditis with effusion. Dilatation of both ventricles. Multiple splenic, renal and suprarenal infarcts. Chronic passive hyperemia of lungs, liver, kidneys, stomach, intestines. Bilateral apical pleural scars. Fibrous adhesions right pleural cavity. Purulent bronchitis. Pulmonary edema. Caseation of tracheobronchial lymph glands. Acute follicular hyperplasia of spleen.

Case 2. A case of probable *Staphylococcus albus* endocarditis superimposed on the margin of a ventricular septal defect and aortic valve. An 18-year-old white boy was brought to the Roosevelt Hospital by ambulance on September 18, 1939, with the history of recurrent drenching night sweats and syncope. En route he vomited several times and in the Reception Ward had several recurrences of syncope. In the past it had been noted that he had frequent nose-bleeds and an occasional sore throat, but no history of rheumatic fever or its equivalents could be elicited. There was a history of "leaky valves." There were past episodes of precordial pain, ankle edema and dyspnea. On physical examination moderate elevation of temperature was noted. The heart was slightly enlarged. The rhythm was irregular, the rate about 20 per minute. There was a loud systolic murmur heard best to the left of the sternum over the pulmonic area. Blood pressure was 94 mm. Hg systolic and 76 mm. diastolic. Spleen could not be palpated. Liver was just palpable at costal margin. Testicles

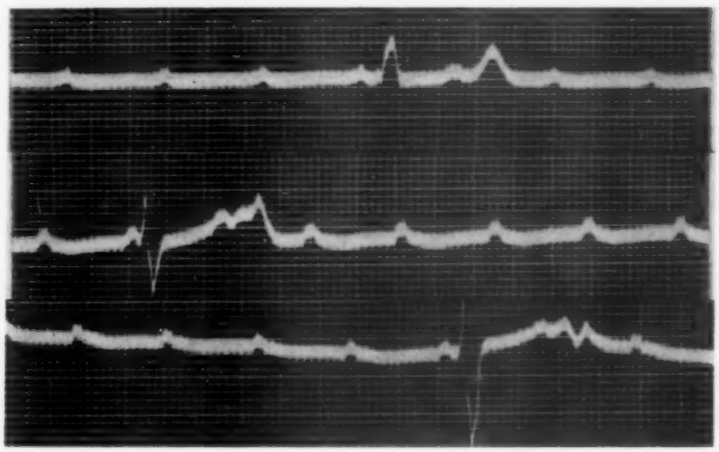

FIG. 2. Electrocardiogram showing complete A–V dissociation. Leads I, II, III, from above downward.

were in the inguinal canal. Urine showed a trace of albumin. Hemoglobin and erythrocyte values were normal. Slight leukocytosis was present. Blood urea was 21.6 mg. per 100 c.c. blood. Several of numerous blood cultures showed *Staphylococcus albus.* Widal was negative. Roentgen-ray showed the heart to have a globular con-

tour and to be slightly increased in the transverse diameter with enlargement predominantly of the left ventricle. Electrocardiogram on day of admission showed complete auriculoventricular dissociation. The auricular rate was 123 and the ventricular rate was about 16 (figure 2). A diagnosis was made of congenital heart disease, probable ventricular septal defect, complete heart block, Adams-Stokes syndrome, probable subacute bacterial endocarditis. On admission and for several days thereafter he received numerous injections of adrenalin and atropine with occasional increase in pulse rate, though without restoration of normal sinus rhythm. He was then given injections of adrenalin-in-oil, 1 c.c. every day for five days without effect on the rhythm. On the sixth day, in addition to the injection of adrenalin-in-oil he received barium chloride 0.060 gm. On the seventh day he received adrenalin-in-oil and barium chloride, 0.120 gm. For the next three days barium chloride was given without adrenalin, in doses of 0.060 gm., 0.060 gm., and 0.030 gm. respectively. On the third day after the barium was started the electrocardiogram showed a regular sinus rhythm (figure 3). During the fourth week after admission several chills with

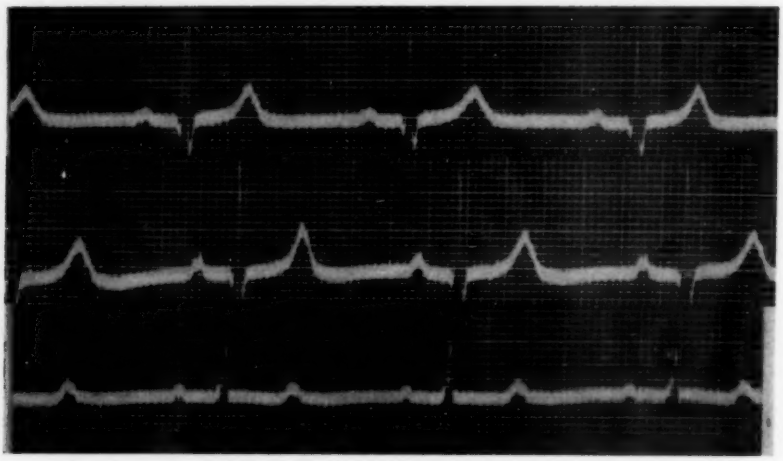

FIG. 3. Electrocardiogram showing normal sinus rhythm.

temperature spiking to 106° F. were noted. Spleen became palpable and soon after that it was noted that the tip of the right index finger was tender. From this time until his death, three weeks later, his course was characterized by spiking temperature and chills. Just before his death a loud blowing diastolic murmur was noted for the first time over the precordium. Permission was obtained for autopsy excluding examination of the brain.

Summary and Findings. The heart weighed 500 gm. The interventricular septum presented a rounded defect at the base measuring 4 mm. in diameter (figure 4). The surrounding endocardium was smooth and glistening on the side of the right ventricular chamber, but on the left side one noted along its anterior margin a firm, pink vegetation which measured 1 by 2 by 1 cm. It was not easily separated from the underlying endocardium. The cusp of the aortic valve situated immediately above the vegetation revealed a perforation approximately 3 mm. in diameter. The remaining aortic cusps were normal in appearance and number. The aortic valve measured 7 cm.

Microscopic Examination. Sections through the myocardium revealed slight fibrosis, some hypertrophy of muscle fibers, and slight brown pigmentation. Section

through the margin of the defect to which the vegetation was attached revealed the latter to be made up of homogeneous, pink-staining, finely granular material, with interlacing strands of fibrin and scattered polymorphonuclear leukocytes. The margin of the defect to which the vegetation was adherent consisted of a central core of dense connective tissue, rather poor in cells, flanked on both sides by a layer of granulation tissue, rich in thin-walled capillaries, and fibroblasts, with scattered polymorphonuclear leukocytes and mononuclear cells. Sections through a block of tissue cut from the upper margin of the septal defect and carried for a centimeter upward to

FIG. 4. Heart showing ventricular septal defect, a large vegetation on the defect-margin aortic valve leaflet.

include the auricular septum showed the cardiac muscle to be made up of bundles of fibers separated by dense connective tissue in which cells were very rare. A small amount of connective tissue separated the individual muscle fibers. These fibers appeared usual in structure. The cell-poor connective tissue appeared focally hyalinized. Just above the septal margin was noted a discrete bundle of rather narrow fibers with dark-staining nuclei and eosinophilic cytoplasm. This was identified as the bundle of His. It exhibited fibrosis and focal degeneration of muscle fibers. The bundle was separated from the main body of interatrial myocardium by a wide zone of dense fibrous connective tissue, poor in cells, and focally hyalinized. The aortic vegetation presented the same appearance as that springing from the defect margin.

Smears from the vegetation revealed gram-positive coccal organisms. Culture of heart's blood revealed *Staphylococcus albus*.

Comment and Discussion

Bacterial endocarditis is a condition occurring most frequently in hearts which have been affected by rheumatic fever, and less frequently in hearts with congenital defects such as bicuspid semilunar valves, ventricular septal defect, or patent ductus arteriosus. Maude Abbott [1] points out the great danger of acute or subacute bacterial endocarditis or endarteritis developing in individuals with cardiac anomalies. She notes that fibrosed semilunar valves or the margins of septal defects are particularly vulnerable. Of 555 cases of congenital heart disease analyzed by her, 98 or 17.6 per cent presented an endocarditis. Of these, 40 per cent were in defects of the base of the ventricular septum such as presented by our second case, and 45 per cent in cases with bicuspid aortic valves, such as presented by our first case. Congenitally bicuspid aortic valves are particularly susceptible to superimposed infection as shown by Lewis and Grant [2] who report 11 cases of bicuspid aortic valves, seven of which showed the presence of bacterial endocarditis. In Abbott's 32 cases of bicuspid aortic valves, 13 died of acute endocarditis of which nine were bacterial. Osler [3] reported 18 cases of bicuspid aortic valves, seven of which showed recent vegetations. As a rule one segment of a bicuspid aortic valve is larger than the other and often shows evidence of fusion of two segments. [4] These points are well illustrated in our first case.

The first case presented was that of a 36-year-old white male. In Abbott's cases the average age noted was 33 years, and males predominated in proportion of 13 to 1. Wauchope [5] in a series of 52 cases in 9966 autopsies noted a predominance of males in the proportion of 3 to 1. Though the facts that the patient had a bacterial endocarditis and that his aortic valve was involved were fully recognized, the basic nature of the valvular defect was not suspected. The importance of a correct diagnosis of the basic defect is purely academic, though it is noted that the most devastating effects are seen where bacterial endocarditis occurs on a bicuspid valve.

The occurrence of pericarditis in this case deserves brief mention inasmuch as it is quite rare as a complication of bacterial endocarditis as pointed out by Libman,[6] and by Thayer [7] in his exhaustive treatise on endocarditis. The latter points out that the diagnosis is rarely made clinically.

The pathogenesis of the pericarditis cannot be stated with certainty. Coronary occlusion with myocardial infarction is often accompanied by pericarditis. The infarction in our case involved the entire thickness of the wall and the pericarditis was very likely the result of this. The diffuseness of the pericarditis and the hemorrhagic exudation may have been related to the fact that the embolus was infected and to the probable presence of bacteria in the myocardium (which in the infarcted area was gray-green in color) in spite of the fact that bacterial stains failed to reveal them.

In Maude Abbott's series of 62 cases of ventricular septal defect, 50 had defects at the base of the septum as illustrated in our second case. Of these, 21 had acute endocarditis, of which 13 died of bacterial endocarditis. Fourteen showed a chronic lesion. Heart block due to or dependent upon a congenital anomaly of the heart is rare, although Yater and his co-workers,[8, 9, 10] who have written extensively on the subject, point out that it is not so rare as formerly supposed. The acquired form of heart block on the basis of a congenital anomaly[11] is even rarer. Up to 1934 a careful search of the literature by Yater failed to reveal any detailed report of acquired heart block due to or directly associated with a congenital anomaly of the heart. Yater reported the first case with complete histopathologic examination. The bundle of His was smaller than normal in diameter and ran along the free edge of the interventricular septum. A short distance from its origin it became fibrotic, and Yater attributed the fibrosis to strain and not infection. The bundle in our case was fibrotic and showed focal degeneration.

The absence of a history of syncopal attacks in our case prior to the onset of the present illness and the resumption of normal sino-auricular conduction before death preclude the possibility that complete block existed prior to the present illness.

The presence of a vegetation in close proximity to the bundle would indicate the possibility of direct involvement of the bundle in the inflammatory reaction. Since the patient lived for some time after the resumption of normal conduction, all signs of inflammation could have disappeared by the time the patient died. It is also possible that because of its proximity to the vegetation the bundle may have become involved temporarily by inflammatory edema. Which of these two explanations is the correct one cannot be stated; both may have played a rôle. Presumably the barium chloride had nothing to do with the recovery from the block, though conduction along the bundle resumed soon after the administration of the drug, after repeated failure of other drugs to produce this effect. We felt that this was purely a coincidence and that the bundle of His was in some way involved in the infective process, the subsidence of which permitted the resumption of normal conduction.

Summary

1. Two cases of congenital heart disease are presented in which bacterial endocarditis became superimposed on the defect and caused death.

2. One of the cases, that of bicuspid aortic valve, illustrates the devastating effects peculiar to this lesion. The unusual complication of pericarditis and its pathogenesis are discussed.

3. The other case, that of ventricular septal defect, is of exceptional interest, inasmuch as a complete auriculoventricular block developed. The bundle of His exhibited fibrosis and focal degeneration. Resumption of normal conduction occurred before death. The pathogenesis of the block is briefly discussed.

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CASE REPORTS

TUBERCULOUS SPLENOMEGALY; STUDY OF A CASE*

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THE occurrence of tuberculous involvement of the spleen in the course of miliary or advanced tuberculosis of other organs is common.[1, 2, 3, 4] However, extensive active tuberculosis localized in the spleen is rare. When this disease occurs, it usually is associated with lesions of lesser extent in the nearby lymph nodes and in the liver, but the spleen appears to be the disseminating focus. Less than 100 cases of this type of tuberculous splenomegaly are recorded. Not all of them have been studied thoroughly and in many reports the specific characteristics are difficult to evaluate.

We present a case of unusually large splenomegaly due to chronic caseating tuberculosis, together with studies which concern chiefly the hematopoietic tissues.

CASE REPORT

J. M. L., a white male, Swiss, 54 years of age, entered the University of California Hospital on November 8, 1935, complaining of enlargement of the abdomen, fever, sweats and loss of weight and strength. He denied any significant illness in the past. He had traveled extensively in temperate climates throughout the world carrying on his occupation of cook. His father had died of pleurisy at the age of 64, and one sibling had died of tuberculosis at the age of 14. His present illness began about eight months before entry, at which time he noted the onset of progressive enlargement of the abdomen, especially on the left side. During this interval he had three episodes of acute pain in the left upper quadrant of the abdomen which were associated with vomiting. The last episode was accompanied by fever and repeated chills, and persisted for three weeks. He had continuous night sweats and lost 20 pounds in weight.

On physical examination the patient appeared chronically ill. Numerous petechiae were scattered over the back, thighs and arms. There was a salmon-pink blush on the palms and soles. Small discrete inguinal, axillary and cervical nodes were present. Small xanthomata were noted on the eyelids. The thorax was normal and the lungs were clear. The heart was normal. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. The abdomen was moderately distended with gas and fluid. The spleen was ballotable and filled the entire left side of the abdomen. Its incisura was felt opposite the umbilicus. It was smooth except for a small nodule on its anterior surface. The liver was smooth, non-tender, and extended 5 cm. below the right costal margin. Dilated veins coursed longitudinally over the surface of the abdomen (figure 1). Bilateral inguinal herniae were present.

Laboratory Procedures. Urine: normal. Stool: normal. Gastric analysis: abundant free and total acid present. Blood Wassermann reaction: negative. Tu-

* Received for publication November 19, 1940.

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berculin test (with old tuberculin): human, negative; bovine, strongly positive. Takata-Ara reaction: strongly positive. Rose Bengal test: interpreted to indicate moderate impairment of liver function. Plasma cholesterol: 212 mg. per 100 c.c.

A roentgenogram of the chest revealed normal lungs. Biopsy of an inguinal lymph node showed no abnormality. Abdominal paracentesis was done, and 36 c.c. of dark red fluid were removed. The fluid had a specific gravity of 1.020 and contained 85,000 erythrocytes and 600 lymphocytes per cubic millimeter. The Rivalta and globulin tests which were done on the fluid were positive. A month later 4000 c.c. of dark red fluid were removed by a second abdominal paracentesis. The fluid had a specific gravity of 1.022 and contained 800,000 erythrocytes and 10,000 leukocytes per

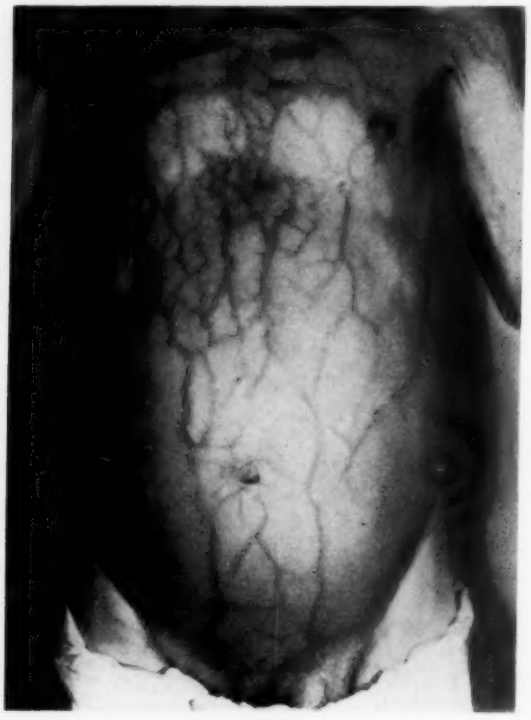

FIG. 1. Infra-red photograph showing collateral venous channels.

cubic millimeter. Culture of this fluid did not show growth, but tuberculosis developed in guinea pigs into which it was injected. The blood studies are indicated in tables 1, 2 and 3.

Course and Treatment. Attempts to stimulate leukopoiesis failed, as can be seen from the tables. A high purine diet was given continuously. Sodium nucleinate of thymus gland was administered in doses of 10 c.c. intramuscularly twice daily for several days. Liver extract (Lederle) was given in daily doses of 3 c.c. intramuscularly on November 9, 10 and 11, and epinephrine in doses of 0.3 c.c. four times daily on November 12 and 13. Abdominal distention was controlled by paracentesis, fluid restriction, and the intravenous administration of salyrgan. No lymph node enlargement developed. Petechiae were constantly present, but no gross hemorrhages occurred. Daily intermittent fever of 38 to 39° C. persisted. On January 20, 1936, the patient

was transferred to the Los Angeles County General Hospital. He pursued a steadily failing course and died rather suddenly on January 27.

Autopsy. (Performed by Dr. J. L. Mason on January 29.) The abdomen was moderately distended and contained 2000 c.c. of turbid red fluid. The parietal peritoneum was smooth, but the visceral peritoneum was covered with thick fibrinous exudate which had accumulated in large quantities beneath the diaphragm and had formed adhesions resembling cobwebs. The left pleural cavity contained 750 c.c. of clear yellow fluid with a specific gravity of 1.010. The pleural surfaces were smooth. The lungs showed passive congestion but no infiltrative lesions or scars. A caseous paratracheal node measured 1.5 cm. in length. The pericardium was red and shaggy

TABLE I

Studies of the Blood

Dates	Nov. 9	Nov. 10	Nov. 12	Nov. 13	Nov. 21	Nov. 22	Nov. 27*	Dec. 18
Hemoglobin (gm.)	14.0				13.5		14.0	15.5
Erythrocytes† (millions)	4.62				4.54		4.58	5.2
Leukocytes	1350	1500	1100	950	1200	950	1350	1100
Neutrophiles	58	68	66	60	62	66	59	
Filament cells	36	48	34	43	52	58	47	
Non-filament cells	22	20	32	17	10	8	12	
Lymphocytes	38	22	26	35	32	34	37	
Monocytes	4	9	2	3	4	0	3	
Eosinophiles	0	0	0	0	2	0	0	
Basophiles	0	1	2	2	0	0	2	
Normoblasts	3	6	2	5	12	0	6	
Platelets	200,000			140,000				
Reticulocytes	12%							
Sedimentation time Linzenmeier technic	95 min.							
Fragility	.40–.35							
Bleeding time Duke's method	19 min.			6 min.				
Clotting time	6 min.	8 min.						
Icterus index					9.7			

* Venous blood was used.

† Well marked anisocytosis, poikilocytosis and slight polychromatophilia of the erythrocytes were observed.

TABLE II

Adrenalin Test

Injection Nov. 8. 1 c.c. 1/1000 Epinephrine HCl Intramuscularly

	Before Injection	30 Minutes After Injection	50 Minutes After Injection	90 Minutes After Injection
Total leukocytes	1200	1600	800	900
Neutrophiles	50	38	45	51
Filament cells	24	30	25	24
Non-filament cells	26	8	20	27
Lymphocytes	30	40	40	31
Monocytes	20	22	13	18
Eosinophiles	0	0	1	0
Basophiles	0	0	1	0
Normoblasts/100	4	0	0	4
Parasites	0	0	0	0
Platelets	Abundant			Abundant

TABLE III

Study of Material from Sternal Marrow and Spleen Puncture

	Sternal Marrow		Spleen Puncture November 26
	November 9	November 25	
Neutrophiles	45.33	39	18
Filament cells	14.00	11	10
Non-filament cells	31.33	34	8
Lymphocytes	31.00	27	30
Monocytes	7.33	12	24
Eosinophiles	0	0	0
Basophiles	0	1	0
Myelocytes	16.33	7	0
Premyelocytes	0	4	1
Myeloblasts	1.00	4	4
Normoblasts	8.66	6	11
Endothelial leukocytes	0	0	12
Polychromatophilia	Moderate	Increased	Marked

and firmly adherent to the parietal pericardium around the base of the heart. There was no excess fluid, and the heart was not abnormal.

The spleen was greatly enlarged, measuring 29 by 18 by 9 cm. and weighing 2700 gm. (figure 2). Its lower pole was opposite the left iliac crest. Its outer surface was smooth, dark red in color and covered with fibrinous material. A large, firm, white area measuring 9 by 6 by 4 cm. and grossly resembling a large infarct was situated at the upper pole. On section the surfaces were dark red, somewhat fibrous and showed no definite pattern. The white area was surrounded by numerous small areas of similar tissue measuring 2 mm. in diameter and extending for some distance into the substance of the spleen. No abnormality was discovered in the splenic vein and artery. The lymphatic system was grossly normal except for large pearly-white lymph nodes at the porta of the liver.

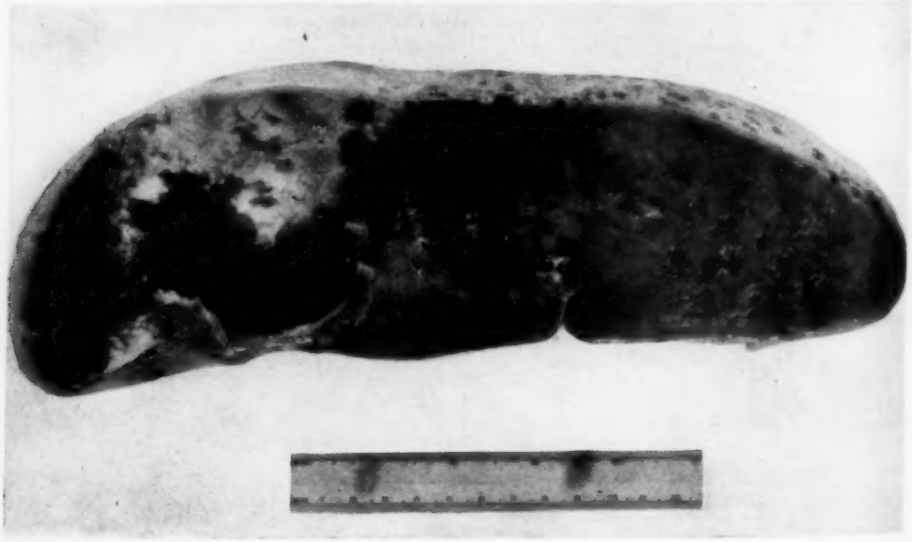

FIG. 2. Gross section of spleen.

The liver weighed 2050 gm. Its surface was covered with fibrinous exudate. On section the normal lobular markings were visible. In addition myriad pale gray nodules averaging 3 mm. in diameter and appearing as focal necroses were noted. The portal vein and its tributaries were slightly dilated but not otherwise abnormal.

Microscopic Examination. Spleen: The capsule was thickened. The normal architecture was altered and the Malpighian follicles were small and indistinct. The reticulum appeared active. There were many agminations of brown pigment. The pulp sinuses were patulous and the pulp cords were filled with red blood cells. Some of the trabeculae were thickened. In some areas the splenocytes were filled with brown pigment. A large anemic infarct surrounded by an area of marked hyperemia was observed. There were small collections of polymorphonuclear cells as well as many small areas of tuberculous necrosis with giant cell formation. The section stained with carbolfuchsin demonstrated myriad acid-fast bacilli singly and in groups which were distributed throughout all portions of the section but in greatest numbers in the areas of necrosis (figures 3 and 4).

Liver: The liver showed small areas of tubercle formation with necrosis. The regularity of the lobular structure was impaired. Some of the parenchymal cells contained two nuclei. The triangular spaces were distinct and in some of them was seen diffuse infiltration of uninucleate cells of the phagocyte series. There were a few polymorphonuclear cells adjacent to the triangular spaces. Small particles of brown pigment were present in the sinusoids. Giant cells were observed in some areas of necrosis (figure 5).

Comment

This case presents the chronic form of massive caseating tuberculosis of the spleen. The important clinical features were: evidence of chronic infection with intermittent fever, occurrence of petechiae, extreme splenomegaly, moderate hepatomegaly and acites, and a gradual failing course which progressed to death nine months after onset of the recognized symptoms.

The blood showed no anemia or polycythemia (table 1), but normoblasts were constantly present. There was marked leukopenia with an absolute reduction in the total number of all white cells. Attempts to increase these failed. After intramuscular injection of 1 c.c. of epinephrine HCl, the total number of leukocytes increased from 1200 to 1600 per cubic millimeter in 30 minutes but then decreased to 800 per cubic millimeter in 50 minutes. The leukopoietic tissues were apparently unable to respond to this injection with the usual leukocytosis.[5] Sternal bone marow was obtained on two occasions by needle puncture (table 3). The specimens revealed a moderate increase in the immature myeloid elements and a slight diminution in the number of nucleated red blood cells.[6] Material obtained from the spleen by puncture showed immature myeloid elements and normoblasts which suggested the presence of hematopoiesis in the spleen (table 3). Tuberculin tests were positive with bovine but negative with human old tuberculin. The ascitic fluid contained tubercle bacilli; these were not differentiated as to strain.

Autopsy revealed a spleen weighing 2700 gm., one of the largest tuberculous spleens on record.[4, 7, 8, 9] Tubercle bacilli were demonstrated in the microscopic section of the spleen. One small caseous lymph node in the mediastinum and many small tubercles scattered throughout the liver were the only other areas of tuberculosis discovered.

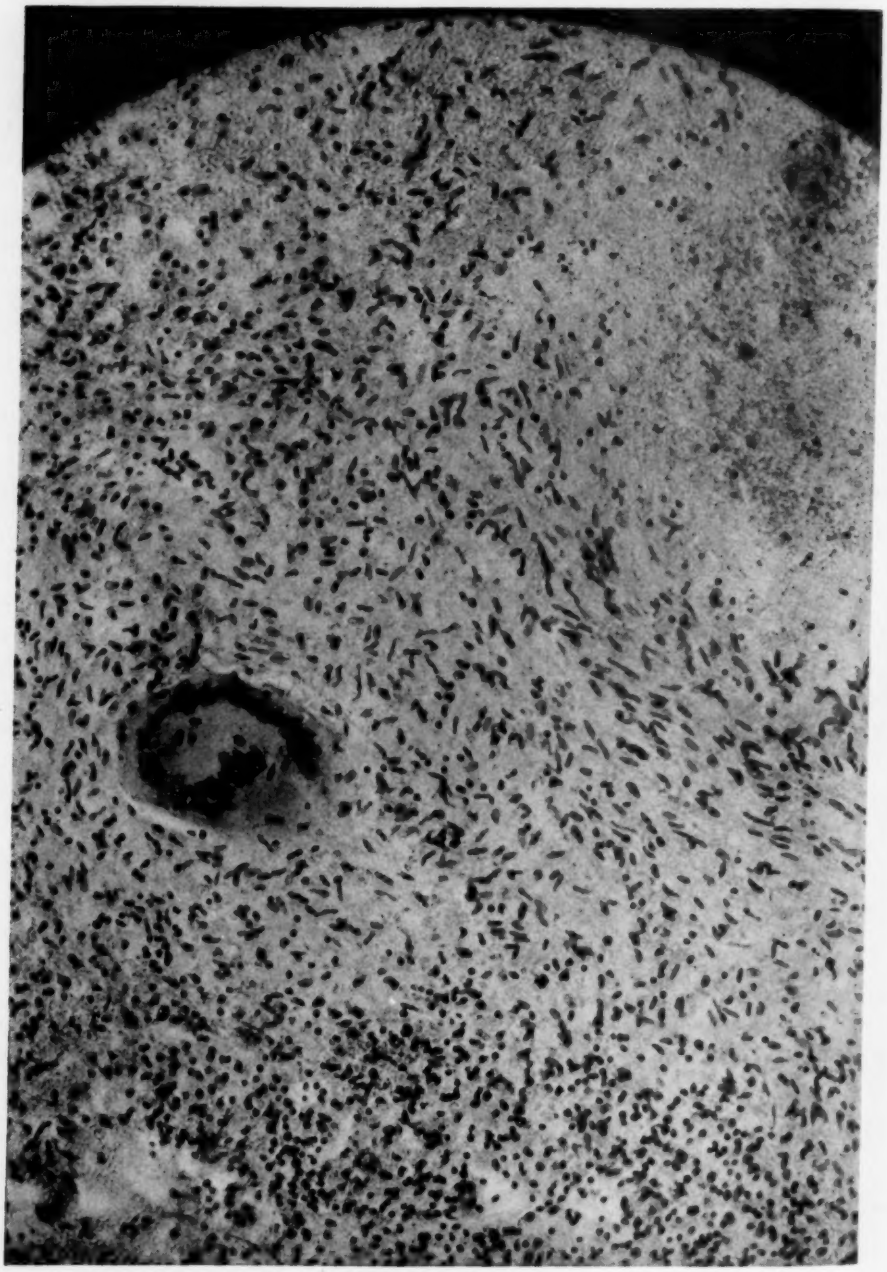

FIG. 3. Photomicrograph of spleen showing tuberculous necrosis and giant cell formation.

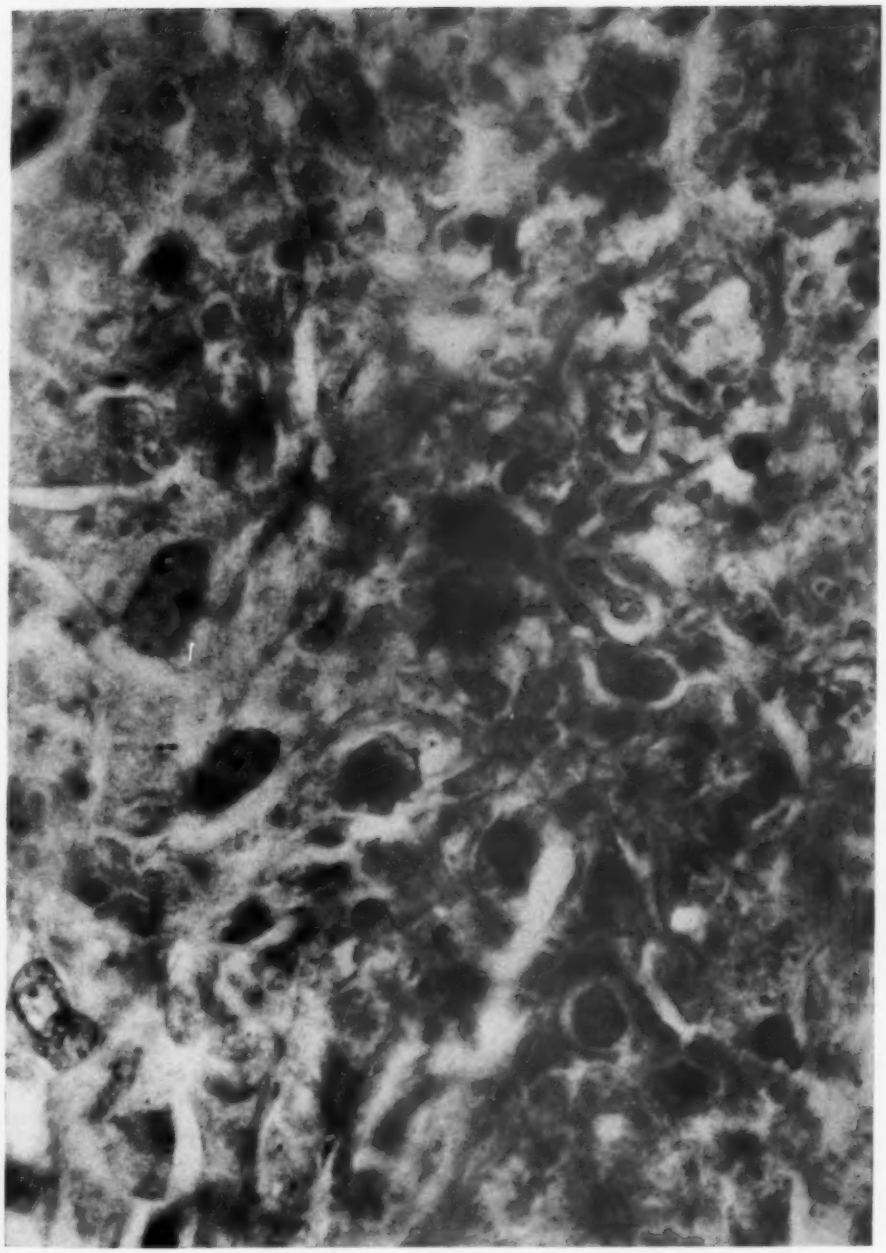

FIG. 4. Photomicrograph of spleen showing tubercle bacilli.

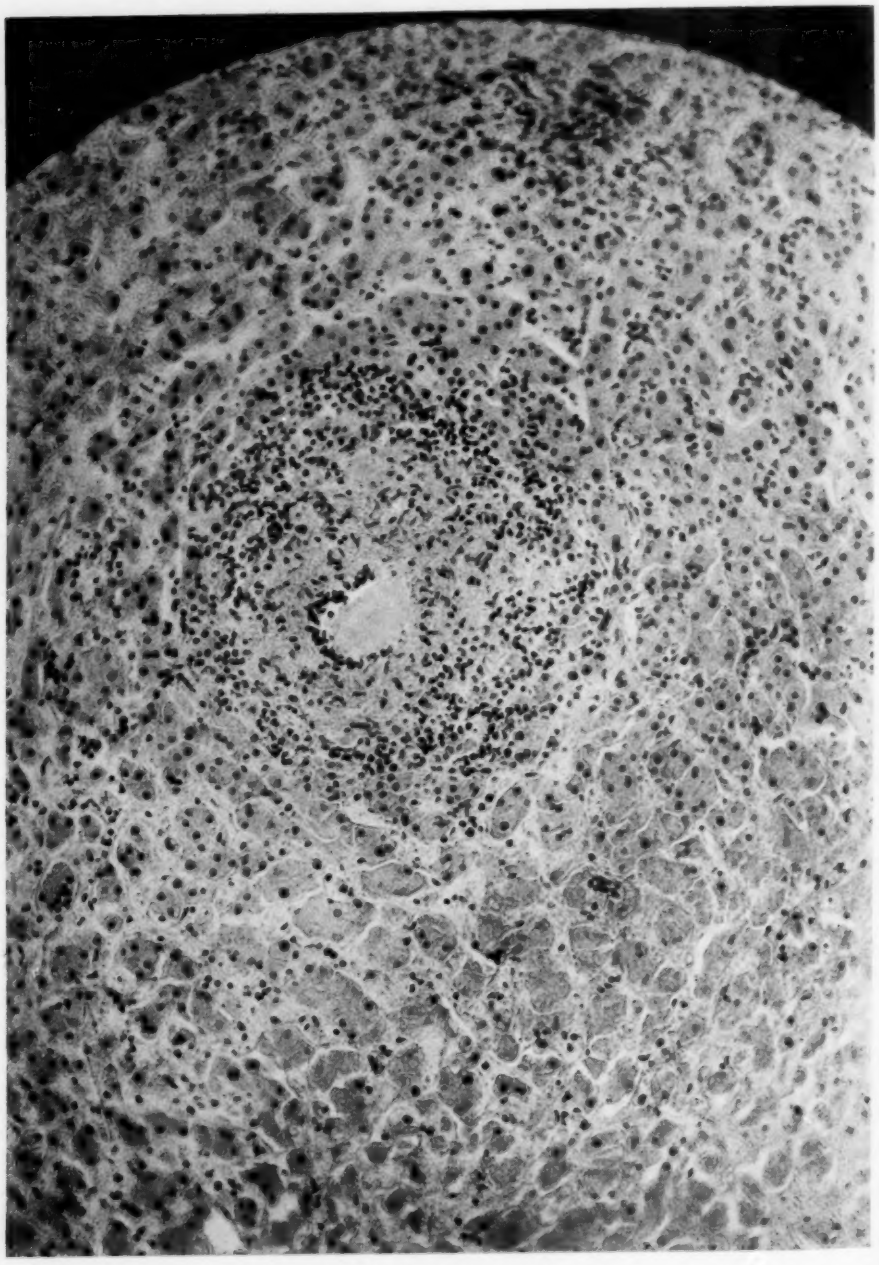

FIG. 5. Photomicrograph of the liver showing an area of necrosis.

Discussion

In the course of tuberculosis of the spleen, abnormalities almost always occur in the blood and the blood forming organs. The mechanisms which operate to bring about these changes remain obscure. The subject has been discussed recently by Engelbreth-Holm.[9] A study of the reported cases does not reveal any uniform blood picture. Anemia, polycythemia, leukopenia, leukocytosis, normal erythrocyte count and normal leukocyte count have all been observed in cases of tuberculous splenomegaly.[1, 2, 3, 4, 7–21] Anemia with leukopenia or normal leukocyte count is most frequently observed. Hemorrhages from the gastrointestinal tract or purpura sometimes occur.[4, 7, 8, 9]

Erythrocyte and hemoglobin values were normal in the case reported. However, the elevation of the icterus index, the increase in reticulocytes, the presence of normoblasts in the spleen and blood, the polychromatophilia and the variation in the size and shape of the red blood cells were suggestive of increased destruction of red blood cells. A profound leukopenia was associated with a slight increase in non-filament neutrophilic cells in the blood and an increase also in immature myeloid elements in the bone marrow. The presence of immature myeloid elements and normoblasts in the spleen suggested active hematopoiesis in this organ. These abnormalities in the hematopoietic tissues apparently resulted from extensive disease of the spleen.

Summary

The clinical, laboratory and autopsy findings of a case of localized tuberculosis of the spleen are presented. The clinical characteristics were a gradually failing course with intermittent fever, petechiae, extreme splenomegaly, hepatomegaly and ascites. Autopsy revealed a very large tuberculous spleen in which tubercle bacilli were demonstrated. The only other areas of tuberculosis discovered were small patches of tuberculous necrosis in the liver, caseous nodes at the porta of the liver and one caseous paratracheal node. Extreme leukopenia persisted in spite of attempts to increase the number of circulating leukocytes. The immature myeloid elements in the sternal marrow were increased, and there was evidence of hematopoiesis in the spleen. Anemia did not occur.

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PSITTACOSIS; REPORT OF A FATAL CASE TREATED WITH SODIUM SULFAPYRIDINE*

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New York, N. Y.

Prior to the epidemic of 1929–1930 psittacosis was almost unknown in this country except for a few sporadic cases. It has, however, been recognized as a disease, and the association with parrots noted, for at least 60 years. Its infrequency in recent times has tended to cause it to be almost forgotten. Many cases have undoubtedly gone unrecognized and were considered to be atypical typhoid, influenza, or influenzal pneumonia. It has seemed worthwhile, therefore, to present the following case and to call attention again to this disease.

Case Report

S. B., a woman aged 44, entered Sydenham Hospital, April 15, 1940, complaining of pain and swelling in the perianal region, associated with a purulent discharge and itching, of several months' duration. She had had no previous illnesses of importance.

Physical examination disclosed a well developed and well nourished woman, not appearing acutely ill. The pupils reacted to light and accommodation. There was no

* Received for publication September 24, 1940.

nasopharyngeal congestion. The lungs were clear. The heart showed no abnormal findings. The spleen was not felt. The extremities were normal. The reflexes were all active. Rectal examination showed the presence of a simple fistula in ano at the posterior commissure. The rectal temperature was 100.4° F., the pulse 88 and the respirations 22.

On April 16 the fistula was excised under general anesthesia.

On April 19 the patient complained of pain in the neck and in the joints. The temperature rose to 102° F. The operative wound looked clear and appeared to be healing satisfactorily. The lungs remained clear. Nothing definite could be found to account for the fever, which continued to mount, with remissions, until it reached 104.6° F. on April 24 (figure 1). Additional history obtained at this time revealed

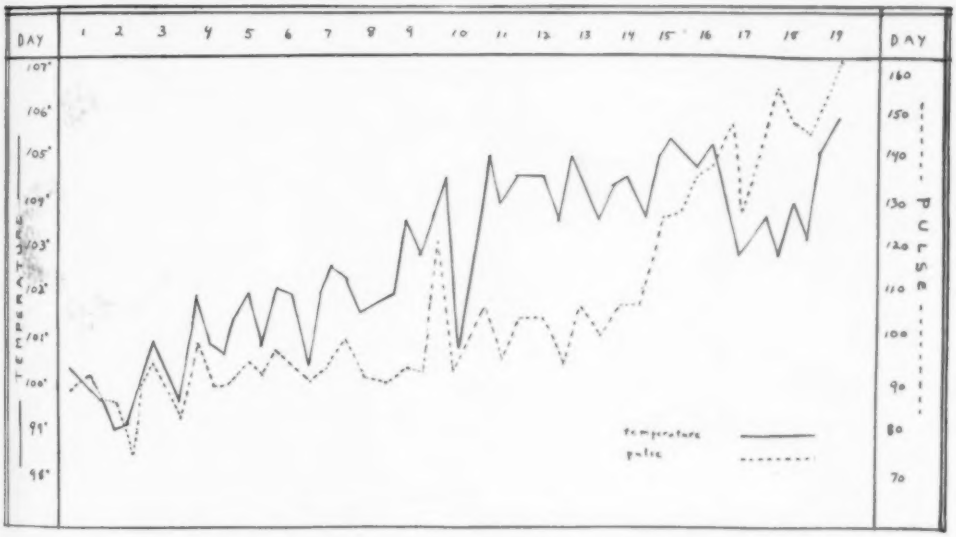

FIG. 1. Temperature and pulse. The pulse is relatively slow in relation to the temperature, except in the terminal phase.

that on April 10 the patient had been bitten on her right index finger by an African love bird recently imported from California and that the bird had died two days later.

On April 26 the patient appeared toxic and markedly apathetic. The temperature was 104.6° F., the pulse 100, and the respirations 24. Except for some paravertebral dullness the lungs appeared clear. The heart showed a relative bradycardia (figure 1) but no murmurs. The spleen was not felt. The joints were normal. There was no adenopathy. The neurological examination was entirely negative. The history of exposure to the love bird suggested the diagnosis of psittacosis. Chemotherapy was begun on this date. The patient received intravenously 10 grams of sodium sulfapyridine in four divided doses. The subsequent daily intravenous dose of this drug was 8 grams.

The urine was essentially negative, except for a very faint trace of albumin. The red blood count was 3,750,000, with 67 per cent hemoglobin. The white blood count was 11,300 with 77 per cent neutrophiles of which 12 were band forms and 65 segmented, 18 per cent lymphocytes, and 5 per cent monocytes. The smear showed no malarial plasmodia. Both aerobic and anaerobic blood cultures were sterile. Agglutination tests for typhoid, paratyphoid, undulant and typhus fevers were all negative.

A roentgenogram of the lungs taken April 25 (figure 2) showed a bilateral pneumonic process, spreading from the hilar region on the right and involving the lower lobe on the left side.

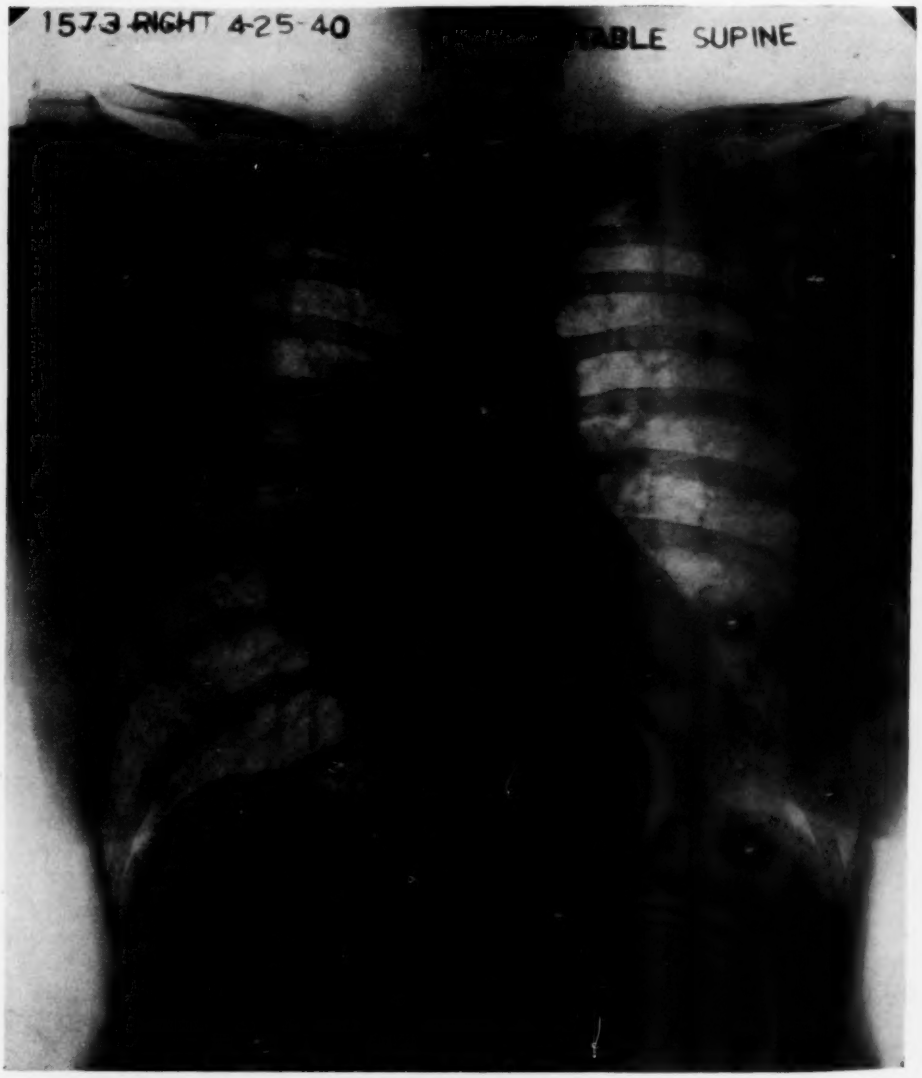

FIG. 2. Appearance of lungs. Note right hilar involvement with spread into the adjacent parenchyma. There is also involvement of the lower left lung field.

A specimen of the patient's blood was submitted to Dr. Karl F. Meyer, of San Francisco, who reported that the serum gave a strong complement fixation reaction with psittacosis antigen in a dilution of 1 to 128. This established the diagnosis of psittacosis.

The patient's condition became progressively worse. The temperature reached 105.6° F. on April 30. She was in a semistupor and markedly dyspneic. Cyanosis

was moderate. There were numerous moist and subcrepitant râles over both lungs. The daily administration of sodium sulfapyridine intravenously was being continued.

The roentgenogram of April 30 (figure 3) showed further extension of the pneumonic process, involving the greater part of the right lung.

FIG. 3. Five days later, further extension of process on right to involve almost the entire lung field.

The blood count showed now 3,150,000 red blood cells, with 58 per cent hemoglobin, and 9,950 white blood cells with 77 per cent polymorphonuclears, of which 17 were band and 60 segmented forms, 8 per cent monocytes, and 15 per cent lymphocytes. The sputum did not show the presence of pneumococci. The blood sulfapyridine level

was 10.3 mg. per cent. The urine showed now 4 plus albumin, 2 plus urobilinogen, a few granular casts, 15 to 20 red blood cells and 6 to 8 white blood cells per high power field.

On May 3 the patient's general condition was very grave. The temperature was 105.8° F., the pulse 170, and the respirations 48. She died the same day.

Autopsy (May 4, 1940; Dr. A. M. Ginzler; 16 hours after death). The body was that of a fairly well developed and well nourished 44 year old white female. The abdomen was moderately distended. There was slight cyanosis of the lips and nail beds. Otherwise, the body presented no noteworthy features externally. The peritoneal cavity contained no free fluid. The peritoneal surfaces were smooth and glistening. The loops of small bowel were slightly distended. The liver margin was 1½ fingers'-breadth below the right costal margin. The spleen was not visible. The abdominal viscera were otherwise normal in appearance. The domes of the diaphragm were at the level of the fourth interspace on either side. The pleural spaces contained no fluid and were free of adhesions. The pleural surfaces were smooth and glistening. The right lung weighed approximately 1125 grams. The right lower lobe was large, heavy and firm throughout except for small areas of subcrepitant consistency at the periphery. On section the cut surfaces were reddish-gray to reddish-brown and, for the most part, dry and granular, obscuring the normal alveolar markings. At the periphery there were areas somewhat moist and congested, and moderately air-containing. The upper and middle lobes contained irregular areas of granular consolidation toward the hilus, and in the remainder showed considerable edema and congestion. The left lung weighed approximately 725 grams. The lower lobe showed almost complete consolidation. The upper lobe was fairly dry and moderately emphysematous. The trachea and bronchi showed considerable mucosal congestion and contained a small amount of frothy fluid. The tracheo-bronchial lymph nodes were moderately swollen. The pulmonary vessels appeared grossly normal. The heart was essentially normal in size and appearance. The pericardial surfaces were smooth and glistening. The chambers and valves appeared grossly normal. The myocardium was moist and reddish-brown; there was no gross evidence of fibrosis. The coronary vessels and aorta were thin, elastic, and of normal caliber. The liver weighed approximately 1300 grams. The capsule was thin and smooth. On section the cut surfaces were uniformly yellowish-tan. The lobular markings were not prominent. The hepatic and portal vessels, gall-bladder and biliary tract showed no gross changes. The spleen weighed 150 grams and was moderately soft in consistency. The capsule showed no thickening. On section the pulp was markedly congested. The follicles were distinct. The gastrointestinal tract showed irregular areas of mucosal congestion throughout. The pancreas showed no gross changes. The adrenals appeared normal. The kidneys weighed approximately 300 grams together. The capsules stripped easily, exposing smooth grayish-brown surfaces. On section the cortices appeared slightly swollen. The cortical and medullary markings were distinct and regular. The pelves, renal vessels, ureters and bladder showed no gross pathological changes. The uterus was moderately enlarged due to several intramural and subserous fibroid nodules. In addition to the tracheobronchial nodes, there was also moderate enlargement of the mediastinal and para-aortic nodes.

Microscopic Examination. The lungs showed extensive pneumonic consolidation (figure 3). The exudate was markedly fibrinous in character and only moderately cellular. The cells consisted chiefly of large macrophages with considerable granular cytoplasm (figure 4). Many contained round, basophilic, intracytoplasmic inclusions. Scattered neutrophiles were present in small numbers. The interalveolar septae were moderately thickened owing to capillary congestion and mononuclear infiltration. Occasionally they were lined by endothelial-like cells with plump nuclei. The pleura remained essentially normal even where overlying pneumonic parenchyma. Other

portions of the lung showed edema and congestion. The bronchi contained a moderately cellular, mucoid exudate, but showed only mild or no inflammatory reaction of their walls. The lymph nodes showed a moderate inflammatory hyperplasia. Many of the sinusoids were crowded with large macrophages of the type seen in the pulmonary alveoli (figure 5). One section showed a small area of necrosis. There were degenerative changes of the liver cells, particularly about the central veins, and a diffuse moderate fat vacuolization. The liver capillaries were dilated. The splenic pulp was markedly congested and showed moderately increased cellularity due to the

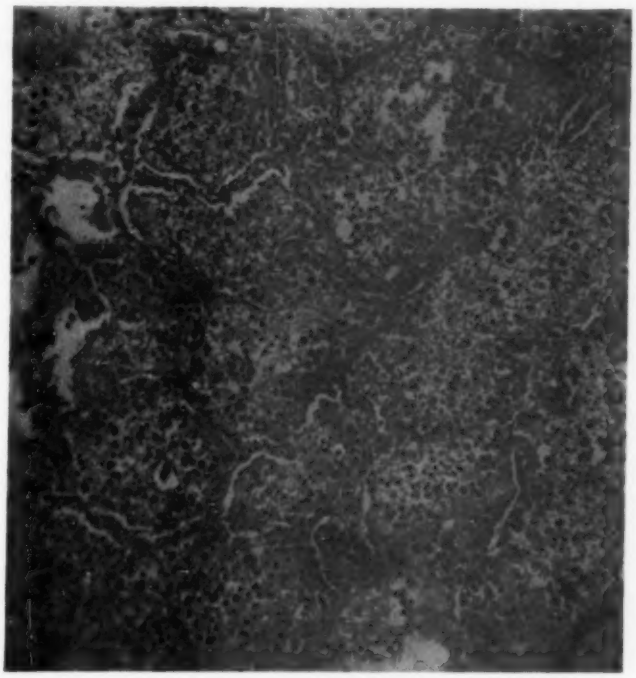

FIG. 4. Section of the lungs under low power (× 100) showing consolidation.

presence of polymorphonuclear, plasma and mononuclear cells. Sections of the remaining organs showed no noteworthy histopathologic features.

Gross Anatomic and Microscopic Diagnoses. Bilateral confluent lobular pneumonia; inflammatory hyperplasia of lymph nodes; fatty degeneration of liver; fibromyomata of uterus.

COMMENT

This case illustrates many of the typical features of psittacosis. The history of exposure to the recently acquired love bird was an important lead in making the correct diagnosis. Indeed, it would be too much to expect that the nature of the infection would be recognized without knowledge of a possible source of exposure. In this connection it is to be noted that all or nearly all birds belonging to the family Psittacidae are actual or potential carriers of the disease. The shell parakeet is regarded as the most important vector of the illness, for the reason that this bird enters into commerce in large numbers.

The investigations of Bedson,[1] Krumwiede,[2] and Rivers,[3] and their respective co-workers, furnish ample evidence that a filterable virus is the etiologic agent of this disease.

The incubation period has been estimated to range from seven to 14 days, although it may occasionally be prolonged to more than a month. In our case it was short, probably eight days.

Except for the pulmonary involvement, our case showed a marked resemblance to typhoid fever. This is a common observation. The patient frequently presents a typhoid-like state, with headache, disorientation and marked drowsiness progressing to stupor. Rose spots may occur about the end of the first

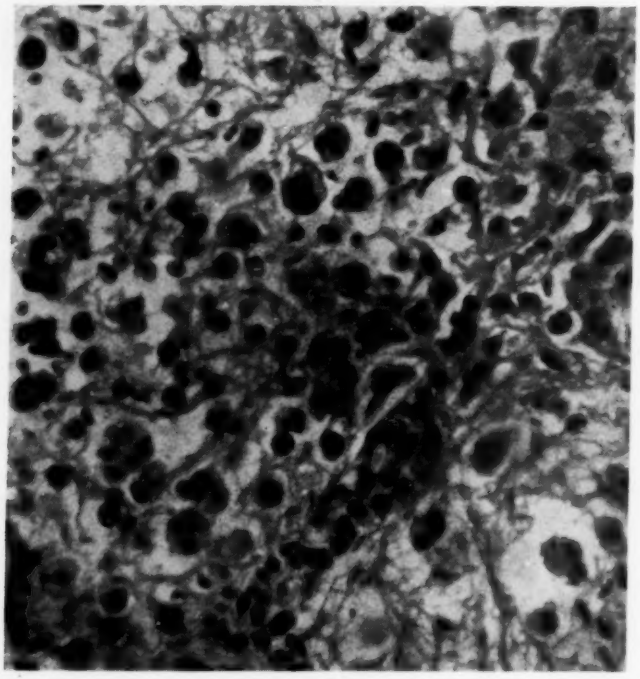

FIG. 5. Section of the lungs under high power (× 500) showing the fibrinous and moderately cellular exudate. The cells are predominantly large mononuclear phagocytes.

week. The spleen, however, is as a rule not palpable. The fever when first recorded is usually 100° to 102° F., and tends to rise to a height of 103° to 105° F. with irregular remissions during the second week. The pulse is likely to be slow in relation to the temperature. This pattern was observed in our case, except in the terminal phase (figure 1), when the pulse became very rapid and feeble.

As a rule, pneumonia develops early and is the most striking feature of the disease. There is usually but little cough or expectoration early, but these may develop later. The cough is usually non-productive. Dyspnea and cyanosis are present only when there is extensive pulmonary involvement. Early there may be very meager or no physical signs in the lungs, although the roentgeno-

gram may show at the time a definite pneumonic process. This was observed in our case (figure 2). As the consolidation spreads to involve a lobe or more, râles and other signs become apparent. It should be noted that in spite of fairly marked pulmonary involvement on April 26, our patient presented no symptoms referable to the chest. There was no increase in rate of respiration, no pain on breathing, no cough and no expectoration.

As shown by our case, the white blood count is usually normal or slightly above normal, but a leukopenia is not infrequent. Our patient had also a moderate anemia. Albuminuria is a very constant accompaniment after the disease is established. This was demonstrated in our case.

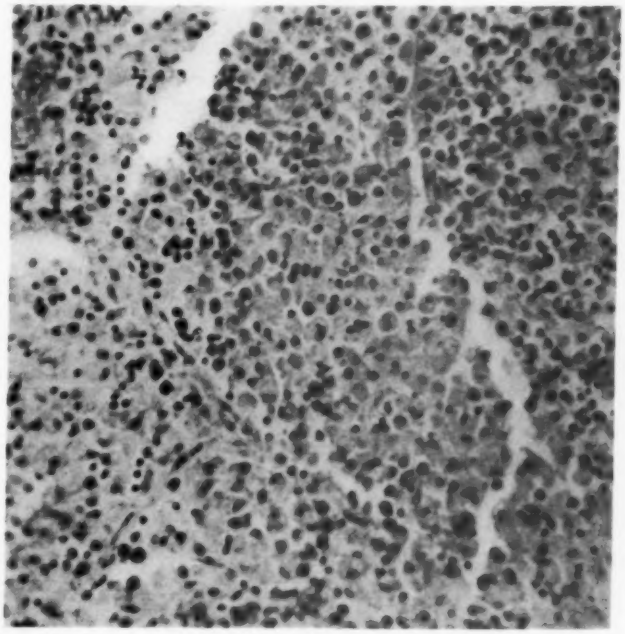

FIG. 6. Medium power (× 250) section of lymph node showing sinusoid crowded with large mononuclear phagocytes.

Bedson [4] was the first to point out that the patient's serum will fix complement in the presence of a psittacosis antigen, and he stressed the value of this reaction as a diagnostic procedure. Rivers [5] and his co-workers demonstrated that the diagnosis can be confirmed also by inoculation of the patient's sputum into white mice. The complement fixation test in our case was strongly positive.

The case fatality rate is generally given as 20 per cent. Extensive pulmonary involvement is regarded as an ominous prognostic factor. Several observers have noted that children and young adults tend to have mild attacks and that deaths are rare in patients under 30 years of age.

Treatment has in the main been symptomatic. Blood transfusions and administration of liver extracts have been recommended. Convalescent serum has been tried by several investigators and found to be of very doubtful value. So

far as we know, this is the first record in this country of the use of sulfapyridine or its sodium salt in the treatment of psittacosis.

The pathologic findings presented by this case of psittacosis were quite typical. The lungs showed the characteristic inflammatory process which is primarily focal or lobular and apparently not closely related to the bronchioles. The alveolar exudate was markedly fibrinous in character and only moderately cellular (figures 4 and 5). The cells were chiefly large mononuclear macrophages with considerable granular cytoplasm. Scattered neutrophiles were present in small numbers. The pleura, as has been frequently observed, was essentially normal. The lymph glands (figure 6) and to a lesser degree the spleen also showed the presence of large macrophages of the type seen in the pulmonary alveoli. The liver showed areas of degeneration, particularly about the central veins. There were no other remarkable changes.

The authors wish to express their gratitude to Dr. Karl F. Meyer, of San Francisco, for his prompt and valuable assistance in establishing the diagnosis, and to Dr. Dana W. Atchley, of the College of Physicians and Surgeons, Columbia University, for valuable suggestions and criticisms.

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TRICUSPID STENOSIS: REPORT OF A CASE WITH INVOLVEMENT OF ALL FOUR VALVES OF THE HEART *

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Tricuspid stenosis is an uncommon valvular lesion of the heart and one rarely diagnosed clinically. Leudet [1] in 1888, J. B. Herrick [2] in 1897, W. W. Herrick [3] in 1908, Futcher [4] in 1911, and Zeisler [5] in 1933 have collected cases. Zeisler could find but 250 autopsied cases in the world literature and of these only 12 per cent were correctly diagnosed before death. Formerly there was discussion as to whether the lesion of tricuspid stenosis is congenital or acquired. For many years the great majority of cases have been considered as due to rheumatic heart disease. About 50 per cent give a history of rheumatic fever. Females are three times more frequently affected than males. The greatest number of those affected die between the ages of 20 and 30. Tricuspid stenosis is rarely present alone. It is usually accompanied by lesions of one or more of

* Received for publication October 9, 1940.
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the other valves. The mitral is most commonly affected so that in the majority of cases tricuspid stenosis and mitral stenosis coexist.

The important clinical signs of tricuspid stenosis are produced mechanically by a diseased valve obstructing the flow of venous blood between right auricle and right ventricle.[6] In an attempt to overcome this obstruction the auricle hypertrophies. Partially failing to overcome it the auricle dilates. This causes dilatation of the vena caval openings into the auricle with the consequent loss of the valvular action of the musculature surrounding them. Then the venae cavae dilate to accommodate the backflow. The result of this mechanism is that the blood in auricle, venae cavae, jugulars and liver is under greatly increased pressure. Lacking the protection against backflow afforded by interposed valves, it pulsates strongly in response to right auricular systole. It also pulsates in response to right ventricular systole. Since tricuspid insufficiency always accompanies tricuspid stenosis, a portion of the right ventricle's blood will be forced into the right auricle, thereby starting a pulse that travels to jugular and liver.

Clinical Findings. (1) Dyspnea on exertion.[7] (2) Cyanosis. (3) Right-sided enlargement of heart. (4) Elevated venous blood pressure. (5) Distention and presystolic pulsation of cervical veins with large "A" wave in phlebogram due to strong right auricular systole. (6) Enlargement and double pulsation of liver, detectable by observation, palpation or hepatogram. One pulsation is synchronous with the "A" wave of jugular pulse and like it is produced by a strong right auricular systole. The other is synchronous with the "V" wave of jugular pulse and like it is produced by right ventricular systole. (7) Disappearance of "A" waves in phlebogram and hepatogram (the double liver pulsation either giving way to a single pulsation or disappearing altogether) upon the failure of the right auricle or onset of auricular fibrillation or nodal rhythm.[8] The single wave or "V" wave of phlebogram and hepatogram is due to tricuspid insufficiency and was called the ventricular form of the venous pulse by Mackenzie.[9] (8) Concomitant mitral stenosis which produces a rough diastolic or presystolic murmur at the apex. The murmur of tricuspid stenosis, also a diastolic murmur, is usually heard over the xiphoid process and may or may not be differentiated from that at the apex. The presence of systolic murmurs at apex and xiphoid may complicate the differentiation. (9) Ascites out of proportion to the peripheral edema and the congestion of the lungs. (10) Cirrhosis of the liver[10] following prolonged chronic passive congestion. Either may give rise to jaundice.[11]

Differential Diagnosis. Chronic constrictive pericarditis and pericardial effusion must be differentiated from tricuspid stenosis. By obstructing venous return to the right auricle they may give rise to high venous pressure, hepatomegaly and ascites. The differentiation should not be difficult because of the normal-sized, quiet and fixed heart of constrictive pericarditis and the pear-shaped heart with weak sounds and paradoxical pulse of pericardial effusion. However, it is worthy of note that an auricular liver pulse has been reported in both these conditions.[12, 13]

To differentiate tricuspid stenosis from tricuspid insufficiency may be very difficult, particularly in the end stages of heart disease. Tricuspid insufficiency will, as long as the right ventricle is strong enough and in spite of the presence of cardiac arrhythmia, give a liver pulse consisting of one big wave in contrast to the two waves of tricuspid stenosis. However, this differentiation holds good

only so long as the patient with tricuspid stenosis has a normal cardiac rhythm. If auricular fibrillation should supervene, the "A" wave of auricular systole, so diagnostic of tricuspid stenosis, would disappear leaving the single "V" wave of tricuspid insufficiency.

Tricuspid stenosis cannot be diagnosed in a case of mitral stenosis before the characteristic double pulsation of the liver appears. It may be suspected in a young girl [14] from the presence of a diastolic murmur at the xiphoid which has different characteristics from the mitral murmur.

Probably the chief reason for the rarity of the diagnosis of tricuspid stenosis is a concomitant cardiac arrhythmia which deprives the right auricle of its ability to contract in systole and give rise to the large "A" wave in the liver pulse.

Case Report

D. F., a 19-year-old unmarried colored girl, was first seen by us on her second admission to Emergency Hospital in May 1938 complaining of swelling of the face, abdomen and legs, shortness of breath, and a cough sometimes productive of bloody sputum. She had been suffering from heart trouble for 21 months and had had several hospital admissions during this time. At the beginning of her illness the important findings had been puffiness of the face, slight ankle edema, coarse râles at the lung bases, an enlarged heart with signs of mitral stenosis, an enlarged liver, a venous blood pressure of 110 mm. of saline and a four plus Kahn reaction. After several months signs of aortic insufficiency had been detected. About nine months before we saw her the presence of a to-and-fro murmur at the tricuspid valve area, a pulsating liver and an elevated venous pressure (235 mm. saline) had led to the diagnosis of tricuspid insufficiency. About a month before we saw her she had pneumonia involving the right lower lung. There was no past history of rheumatic fever, but she had had frequent sore throats. One and one-half years before the onset of heart trouble she had been hospitalized for an acute tonsillitis and at this time heart disease had not been discovered.

The patient lay flat in bed and did not appear acutely ill. There was a visible jugular pulsation. The heart was enlarged to the right and left, with the point of maximum impulse in the fifth interspace nearly in anterior axillary line. Measurements were 13.5 cm. to the left in the fifth interspace and 7 cm. to the right in the fourth interspace. Figure 1 is a roentgenogram of the heart. There was an intense presystolic thrill at the apex. There was a to-and-fro murmur over the entire precordium. At the apex the loudest murmur was a rough, low-pitched, presystolic murmur ending in a blurred first sound. The second sound was obliterated by another softer murmur running through diastole and joining the rumbling presystolic. The beginning and ending of a systolic murmur could not be made out owing to the prominence of the diastolic. Over the lower sternum and upper portion of the liver the rumble gave way to a musical to-and-fro murmur with the diastolic phase of longer duration than the systolic. At the base of the heart A_2 and P_2 were not heard. Here the to-and-fro murmur was faint but the diastolic phase was heard along the left sternal margin and sounded like that of aortic insufficiency. There was no Corrigan pulse. There was a visible and palpable liver pulsation apparently synchronous with the jugular pulsation. The liver was three fingers'-breadth below the costal margin. The heart rate and rhythm were normal, and the lung bases were clear. There was no edema of the extremities, and no ascites.

Venous blood pressure was 345 mm. saline.

Electrocardiographic findings were: Increased P–R interval, 0.23 second. Right axis deviation. A high, broad and split P-wave in Leads I and II. T-wave inverted in Lead III.

Polygraphic tracings were taken of the jugular vein, liver, carotid artery and apex beat of the heart (figure 2). The liver tracing showed two distinct waves, one due to auricular systole and one to ventricular systole. The A–C interval of the jugular pulsation, like the P–R interval of the electrocardiogram, was prolonged. Simultaneous stethographic and electrocardiographic tracings were obtained which showed the characteristics of the various heart murmurs and a P–R interval of 0.28 second (figure 3).

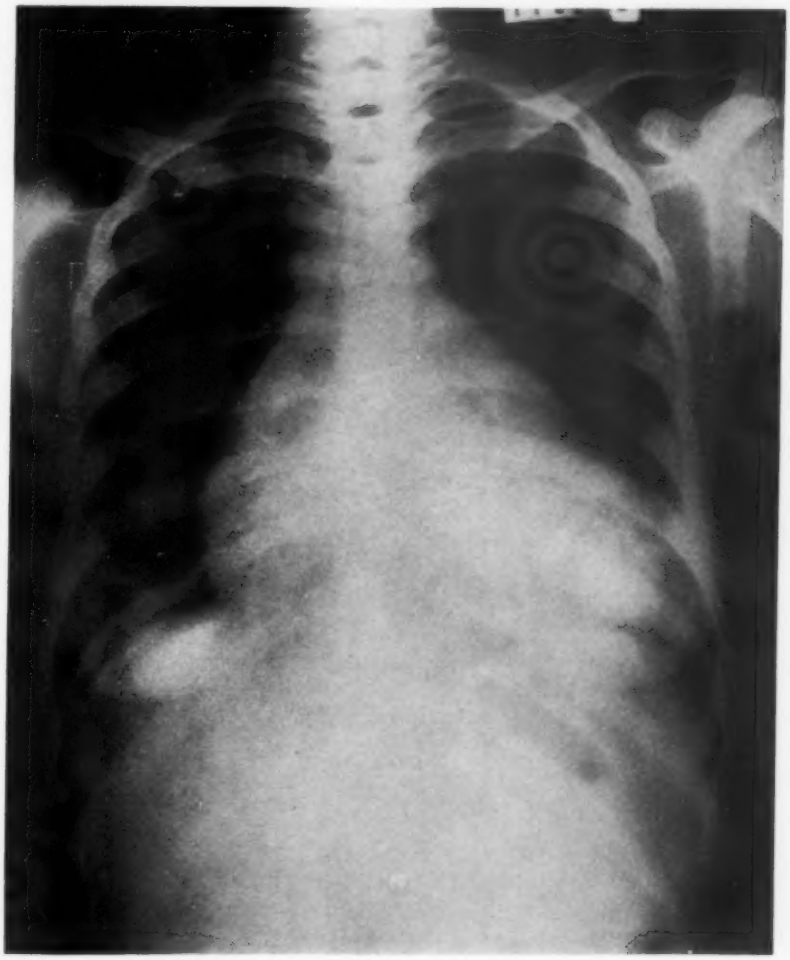

FIG. 1. Teleroentgenogram of the heart.

Several observers later noted that the systolic murmur at the base of the heart was transmitted into the neck vessels, which suggested the presence of aortic stenosis. Complete diagnosis at this time was: chronic cardiac valvular disease (rheumatic); mitral stenosis and insufficiency; aortic stenosis and insufficiency; and tricuspid stenosis and insufficiency.

During the following nine months from June 1938 until her death in March 1939, the patient was bedridden either at home or in the hospital. The heart became tre-

mendous, filling most of the anterior thorax. There was one episode of fever and hemoptysis with consolidation of the right lower lung. There was another stormier episode of tachycardia accompanied by premature contractions. The venous pressure went as high as 400 mm. of saline. The liver remained enlarged and pulsating, and the last few months were characterized by sacral edema and a marked ascites requiring diuretics and paracenteses.

Temperature, pulse and respiration were within normal limits generally except for the episodes of tachycardia and hemoptysis. The blood pressure was 125 mm. Hg systolic and 70 mm. diastolic. Blood counts were not remarkable. The blood Wassermann reaction was four plus and for this reason she received bismuth. Sedimentation rates were within normal limits. Basal metabolism on two occasions was plus 20 per cent and plus 8 per cent. Blood non-protein nitrogen was 28 to 41 mg. per 100 c.c. Kidney function test gave a reading of 72 per cent in two hours. The urine was normal until the last few weeks of life when it showed albumin, casts and red blood cells.

Autopsy. There was some cyanosis of nail beds. The abdomen was distended with fluid, and there was slight edema of the lower extremities.

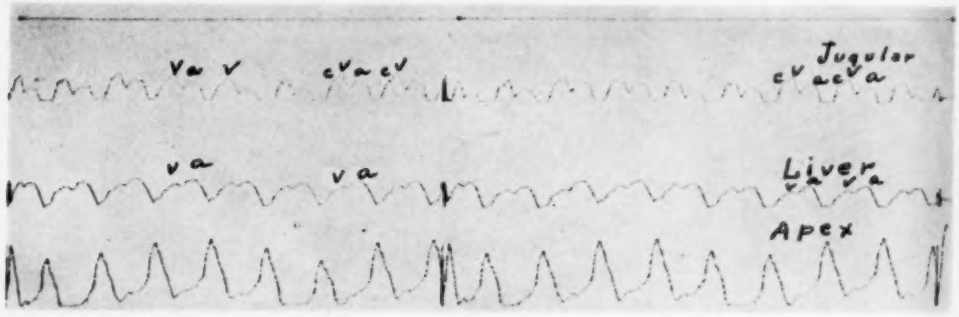

FIG. 2. Polygraphic tracing of jugular vein, liver and apex beat.

The heart was tremendously enlarged, almost filling the anterior thorax. The pericardial sac contained 200 c.c. of clear yellow fluid. The heart weighed 590 grams, the right side being about three times the size of the left. The right atrium was especially large, its musculature tremendously hypertrophied and its endocardium thickened. There was a stenotic lesion of the tricuspid valve which had glued together the three cusps so that they formed a fibrous membrane, the opening of which scarcely admitted the tips of two fingers (figure 4). The right ventricle was not much hypertrophied, measuring 7 mm. in thickness. The free edges of the cusps of the pulmonic valve were involved in a fibrous tissue which thickened them into a rolled edge 1.5 cm. in thickness. A few small intramural thrombi were found in the left auricular appendage. The endocardium of the left atrium was quite thickened. The mitral valve was markedly stenotic with a fish mouth opening which barely admitted the tip of the little finger. The left ventricle was normal. There was a rather marked fibrosis with thickening of all four edges of the aortic valve. There was also some glueing together of the aortic cusps at their bases. The coronary arteries and aorta were normal. The superior and inferior venae cavae were tremendously dilated, the former measuring 4 cm. across and the latter 6 cm.

There was no fluid in the pleural cavities, and there were no adhesions between lungs and pleura. The lungs were gray, subcrepitant, firm, and rubbery in consistency. On sections, they seemed quite dry, and there was no consolidation present.

The abdomen contained about one and one-half liters of clear fluid.

The liver extended 3 cm. below the rib margin. It was heavy, firm and nodular. It was estimated to be one and one-half times the normal weight, although it was not much over normal in size. It showed a variety of colors ranging from orange to red to deep purple. On section it cut with increased resistance. The cut surfaces showed the same variety of colors and numerous radiating scars of fibrous tissue. The venous

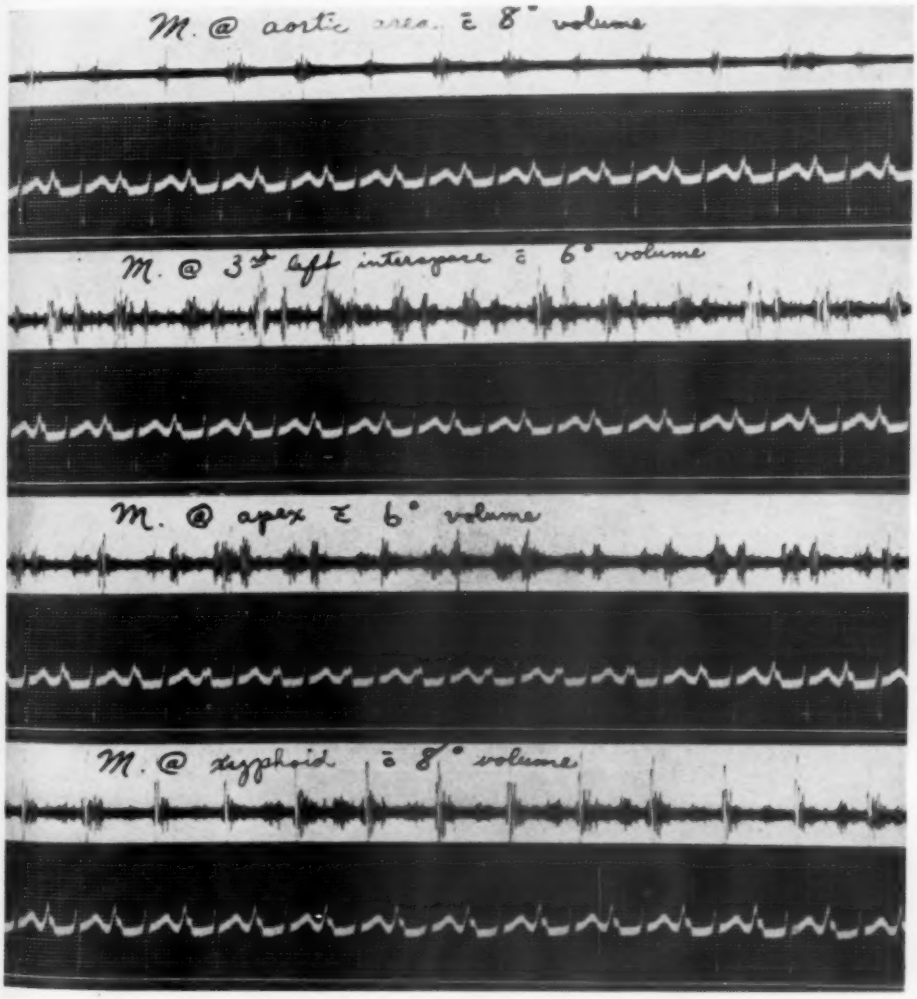

FIG. 3. Simultaneous stethographic and electrocardiographic tracing.

channels were much dilated and very pronounced. There was a lobulated appearance of the tissue and the finger was unable to dent the tissue with ease.

Microscopically there was one area suggesting an Aschoff body in the myocardium. The lungs showed a peculiar interstitial fibrosis recently described as a manifestation of rheumatic fever by Gouley.[15] The liver was in great part destroyed by an intense fibrosis causing an atypical cirrhosis.

Discussion

The progression of the valvular lesions in this patient, as indicated by the change in physical findings during the first year of cardiac symptoms, is interesting, from mitral to aortic to tricuspid. Pulmonic involvement was not diagnosed until postmortem examination. The patient lived for only one and one-

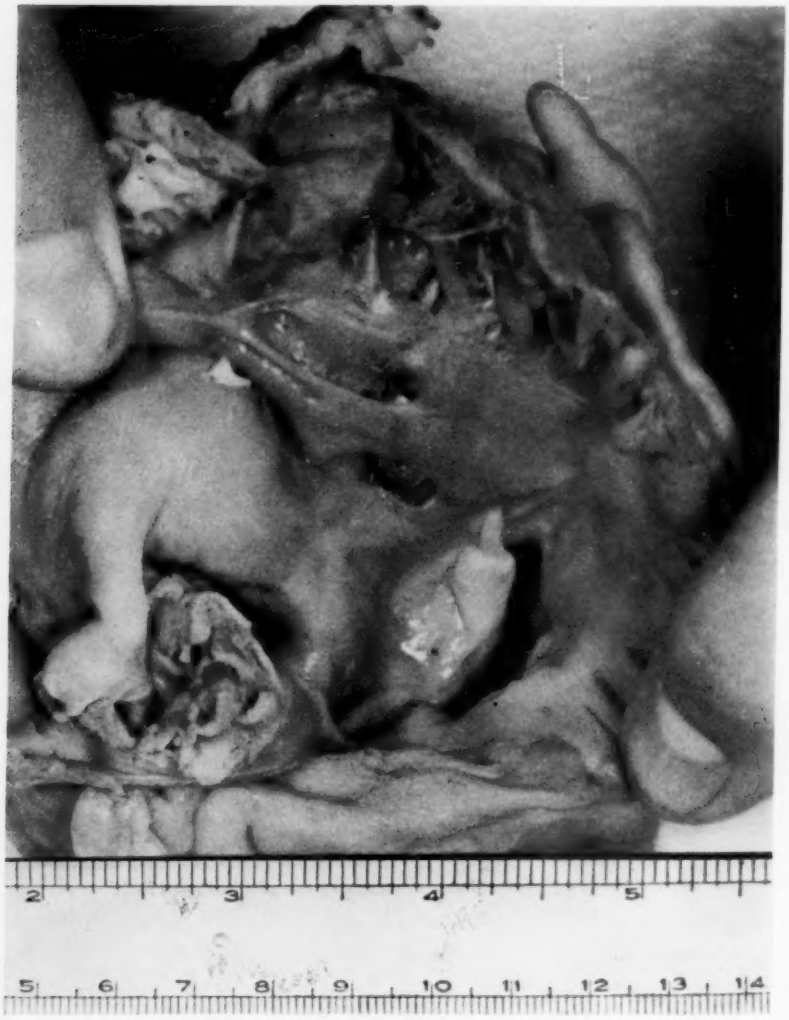

Fig. 4. Photograph of the heart showing tricuspid orifice.

half years after the discovery of tricuspid disease and only two and one-half years after the onset of cardiac symptoms. This is not in accord with the report of Thompson and Levine.[14] They found that patients with tricuspid stenosis, although they get their symptoms at an earlier age, live longer after the onset of symptoms than those who have only aortic and mitral valve involvement. In

their series of 21 autopsied cases of tricuspid stenosis the average duration of symptoms was seven and one-half years.

A very unusual feature in this case is the involvement of all four valves of the heart.

To repeat what has been previously noted by numerous writers, tricuspid stenosis, by decreasing the volume of blood pumped into the pulmonic circulation, relieves the strain on the left auricle and thereby mitigates the signs of concomitant mitral stenosis such as dyspnea, accentuated pulmonic second sound, and congestion of the lung bases.

Ascites out of proportion to edema of the lower extremities is characteristic of constrictive pericarditis as well as tricuspid stenosis. Apparently, the portal circulation is more vulnerable to elevated venous pressure than the vena caval. The reason for this is not clear. In the later stages of both diseases a cirrhosis of the liver consequent upon chronic passive congestion better explains this phenomenon. Chronic passive congestion of the liver accounts for the jaundice which combined with cyanosis may give persons with tricuspid disease a peculiar yellow-blue color.

Summary

Tricuspid stenosis has been discussed mainly from the diagnostic point of view and a case with autopsy reported illustrating the important signs of this disease. Incidentally, all four valves of the heart were affected by the rheumatic process.

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CHOREA COMPLICATING POLYCYTHEMIA VERA; REPORT OF A CASE *

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ERYTHREMIA, or polycythemia vera, is a disease characterized by an increase in the erythrocyte count and volume of the circulating blood, splenomegaly, and various circulatory phenomena due to the increased viscosity of the blood. Neurological symptoms and signs are common in this condition as was emphasized by Vacquez and a little later by Osler in their original reports of this disease. Christian [1] emphasized the neurological manifestations of this condition and stated that the failure to keep these symptoms in mind leads to mistakes in diagnosis. In his report of 10 cases of polycythemia vera, headaches and vertigo were the most common presenting complaints. Blurring of vision, scotomata (often scintillating), hemianopsia, diplopia, paresthesia, paresis, paralysis, and speech disturbance were other central nervous system manifestations. He believed that in the earlier stages, the nervous symptoms resulted from simple circulatory disturbances secondary to the increased viscosity of the blood. In the late stages, he contended that cerebral softening or cerebral hemorrhage and local vascular lesions such as thrombosis were often to be found. Brockbank,[2] in an analysis of 56 cases at the Mayo Clinic, pointed out that headache predominated in 33 of these patients, vertigo in 30, general weakness in 15, fullness in the head, paresthesia and mental impairment in 11. Sloan [3] reported the case of a man aged 40, with erythremia, who developed a thrombosis of the Sylvian artery, followed by a subarachnoid hemorrhage. This patient recovered. In another patient reported in his series the presenting complaint was a pruritus of seven years' duration. Adams [4] found in nine cases of erythremia, six patients who presented themselves because of either headache, vertigo or paresthesia.

Chorea, however, as a complication of erythremia is rare. Umney,[5] in 1909, was the first to report such an occurrence. His patient, a 34 year old female, had a red cell count of 9.5 million, and was known to have had erythremia for some eight years. She developed a speech disturbance which rapidly developed into a chorea, followed shortly by thrombosis of the left jugular vein. The

* Received for publication January 21, 1942.
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chorea rapidly cleared but reappeared after one month, this time followed by edema of the lower half of the body, cough, dyspnea, anuria and finally death. The author thought that the chorea was on the basis of cerebral thrombosis. No autopsy was obtained. Pollack [6] referred to a case, reported by Berdachzi in 1909, of a 50 year old woman who developed chorea from which she finally recovered after seven months. Her red cell count at the onset of the chorea was 10.9 million, and after recovery was 9.3 million. Pollack in 1922 reported the third case of chorea complicating this disease. The patient was a 38 year old woman who had complained of headache, vertigo, dyspnea, cyanosis, and blurring of vision for six months. Her red cell count was 8.1 million, the leukocyte count 8,500. This patient developed chorea which involved mainly the upper half of her body, and which lasted two months. Improvement was noted 10 days after roentgen-ray therapy to the long bones was started. This patient also recovered. Pollack believed that the underlying pathology here was either cerebral thrombosis or hemorrhage. In 1922 Doll and Rothschild [7] in Germany cited six brothers and sisters, five of whom had Huntington's chorea. The youngest sister, who did not have chorea, was found to have a red cell count of 6,000,000, and a hemoglobin of 95 per cent. One brother with chorea had a red cell count of 6.5 million, a hemoglobin of 115 per cent, and a firm palpable spleen. Obviously, however, the etiology of the chorea here was entirely different from the first three cases reported above. In the French literature in 1933, Schiff and Simon [8] reported the incidence of chorea in a 78 year old woman known to have had erythremia for at least five years. The chorea developed rather suddenly and was extremely violent. This patient had a red cell count of 6.8 million with a hemoglobin of only 90 per cent. The leukocyte count was 16,000. A lumbar puncture revealed xanthochromic fluid containing many red blood cells and 35 white blood cells per cu. mm. The Pandy test was strongly positive. These authors, too, explained the disturbance on a vascular basis, probably thrombi and hemorrhages in the region of the basal ganglia.

In this paper we wish to present another case of chorea complicating erythremia together with the laboratory data and the autopsy findings.

Case Report

This patient was first seen in 1935 when she was admitted to the hospital suspected of having a fractured pelvis. In the previous 15 years there had been five fractures of the bones of the lower extremities. Examination was essentially negative save for a dusky skin, markedly reddened mucous membranes and a palpable spleen. The red cell count was 9.4 million, white cell count 12,700, and hemoglobin 130 per cent. The bleeding time was 3.5 minutes, clotting time 2 minutes, clot retraction nil, blood sugar 94 mg. per cent, non-protein nitrogen 29 mg. per cent, blood diastase 20 (normal 80 to 150),[9] blood calcium 11 mg. per cent and glycolysis rate 62.8 mg. per cent per hour (normal about 16 mg. per cent per hour).[10] In view of the physical findings and laboratory data a diagnosis of polycythemia vera was made. There were no symptoms specifically referable to this disease, and the patient was discharged without treatment.

On August 21, 1940, she presented herself at the out-patient department complaining of a sore mouth following the extraction of a tooth three weeks previously. Examination was negative except for emaciation, a dusky skin, red mucous membranes, and a palpable spleen. The red cell count was 8.5 million, the leukocyte count 14,900, and hemoglobin 130 per cent. At this time she refused treatment for her polycythemia.

On October 3, 1940, she again presented herself complaining of "nervousness" of six weeks' duration, an ulcer of the mouth for that length of time, and an attack of severe abdominal pain with nausea the day previous. Examination revealed an emaciated 64 year old white female who was extremely hyperkinetic. She did not remain still for longer than a few seconds but was continuously moving her arms, legs, trunk, head, and features in a variety of purposeless, irregular movements. Her speech was explosive and difficult to understand. These movements could be abolished for a moment or so on request, but would invariably return. The skin was dusky; all the superficial veins were full and prominent. The mucous membranes were red. The eyes, ears, nose and throat were negative save for a few very loose and carious teeth, and a shallow ulcer in the floor of the mouth directly under the upper right molars. This was considered to be traumatic in origin. Fundic examination revealed markedly sclerotic arteries and distended veins. The chest was clear except for an occasional crackle at the left base. Abdominal examination revealed a firm, non-tender spleen which could be palpated four fingers' breadth below the costal margin. Neurological examination revealed an extremely hyperkinetic individual. She was in almost continuous motion, her head, eyes, mouth, trunk and extremities all taking part. The movements were irregular, purposeless and at times explosive in character. Speech was infrequent, only a word or two being spoken at a time, was explosive but clearly articulated. She would quiet down remarkably when asked to do so and could even write a short sentence relatively legibly, but in a minute or so the hyperkinesis recurred. She was well oriented as to time, place and person but apparently had little insight into her condition, describing it as "nervousness." She was not unusually concerned about her activity. The cranial nerves were negative and all the deep tendon reflexes were equal, although the knee and ankle jerks were very sluggish. The abdominal reflexes were absent; there were no pathological toe signs. Sensation, so far as it could be tested, did not seem impaired. The essential laboratory data were as follows: red blood count 9.5 million, white blood count 16,500, cell volume 76 per cent, bleeding time three minutes, clotting time one minute, prothrombin time normal, sedimentation rate nil in 24 hours, clot retraction nil in 24 hours, blood sugar 98 mg. per cent, non-protein nitrogen 39 mg. per cent, diastase 10, blood calcium 9.5 mg. per cent, phosphorus 2.9 mg. per cent, potassium 25 mg. per cent, total protein 8.0 per cent, A/G ratio 1.2, glycolysis rate 51.5 mg. per cent per hour, spinal fluid calcium 6.5 mg. per cent (normal 4.5 to 5.5) and spinal fluid protein 52 mg. per cent.

Two days following admission hyperkinesis had markedly abated, though it was still apparent. Examination at this time was essentially unchanged. This state of affairs continued until the fifth hospital day when the motor phenomena reappeared in greater degree than that seen on admission. At this time, too, she could control herself for a minute or so when requested to do so. In order to prevent exhaustion, 5 c.c. of paraldehyde were administered intravenously. She slept for a few hours, but gradually the hyperkinesis reappeared and was still more exaggerated. Intravenous paraldehyde was again given, a nasal tube passed, and fluids, together with small doses of paraldehyde as needed, were given by this route. On the sixth hospital day bronchopneumonia developed. At that time neurological examination was as before save that the knee kicks and ankle jerks were absent as was also the right biceps jerk. Lumbar puncture was repeated. The spinal fluid was found to be slightly xanthochromic and contained 1000 crenated erythrocytes per cubic millimeter of fluid. Her urinary output decreased markedly. In spite of fluids administered parenterally and by nasal tube, the non-protein nitrogen rose to 85 mg. per cent. Venesection produced no change in the picture, the patient getting rapidly worse and dying on the ninth hospital day.

Autopsy was performed 45 minutes after death. Aside from several small pulmonary and mesenteric thrombi the essential findings were limited to the brain. This

was of normal size and consistency and on its surface contained no hemorrhage or exudate. The cortical veins appeared dark and were distended with blood. On frontal section, throughout the brain substance the small vessels stood out prominently because their blood content was greater than normal. What appeared to be small thrombi filled many of them. These vessels stood out more prominently in the white matter, although they were present in the gray matter also. The veins within the ependyma of the lateral ventricle along the septum pellucidum were distended with blood. The ventricles were normal in size and were not distorted. The cerebellum was normal in the gross and on section. The choroid plexus of the fourth ventricle appeared hemorrhagic, and there was a small amount of bleeding into the ventricle.

Microscopic Examination. In general the morphological changes were uniform throughout the sections examined. The meninges were moderately engorged and contained red cells lying free within their meshes, but no large hemorrhagic deposits. The meningeal veins, especially those of larger caliber, were engorged and some of them contained thrombi which filled their lumina. There was a rather interesting lack of uniformity in the character of the arterial structure. Many of the arteries appeared quite normal. Many, however, especially the smaller ones (those dipping into the cortex), displayed a thickening of the media without any intimal proliferation or deposits. Such vessels were scattered within the substance of the brain in various regions. The arteries did not contain thrombi. Within the brain substance, especially in the subpial and subependymal regions, there were many distended and thrombosed veins. Scattered within the substance of the brain there were smaller veins which were thrombosed and filled with rather fresh clots. Around some of these filled veins there was a variable degree of demyelinization, which in some regions was rather pronounced. The basal ganglia and their surroundings shared in the same general pathological processes as described above. With hematoxylin and eosin stain no significant distortion of cortical architecture could be made out. The nerve cells had a normal structure and appearance. This applied to cortex, basal ganglia, dentate nucleus and cerebellum. No acellular areas in the cortex could be identified. Phosphotungstic acid preparations yielded no additional information regarding the general pathological picture.

Comment

A search of the literature has revealed four similar cases of erythremia complicated by chorea, all occurring in females. This case then represents the fifth to be reported to the present time. Of the five females three were middle-aged. The youngest was 34 years old, the oldest 78. Our patient was 64 years old. The etiology of the chorea as it complicates this disease has been thought in the past to be on a vascular basis, namely multiple cerebral thrombi. On the basis of our knowledge of central nervous system physiology chorea has generally been ascribed to some organic derangement involving the basal ganglia. However, the autopsy in this instance revealed widespread involvement of both cerebral hemispheres. The thrombi were located only in the smaller veins, and there was no predilection for these veins to be located in the basal ganglia or the area immediately adjacent. The xanthochromic and sanguinous spinal fluid obtained shortly before death was, of course, explained by the small hemorrhagic area found in the choroid plexus of the fourth ventricle at autopsy. This case was unique in that it represented the first instance reported in the literature of an autopsy performed on a person afflicted with chorea and polycythemia vera.

* * * *

Dr. Louis Tureen assisted in the interpretation of the histological sections of the brain.

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4. ADAMS, L. J.: Polycythemia vera with special reference to the nervous manifestations, Canad. Med. Assoc. Jr., 1935, xxxii, 128.
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EDITORIAL

COCCIDIOIDOMYCOSIS

THE occurrence in man of infection with the fungus *Coccidioides immitis* has been recognized since the description of the first case by Wernicke and by Posadas in Argentina 50 years ago. Many similar cases (of the generalized form of the disease) have since been reported in the United States, over 500 in all, a large majority of whom had lived in the San Joaquin Valley in California. This disease, generally known as coccidioidal granuloma, is characterized by the development of extensive granulomatous and suppurative lesions, most frequently in the lungs, but also in other viscera, in the skin, bones and joints, and occasionally in the central nervous system. Practically any tissue or organ may be involved. The lesions closely resemble those of tuberculosis in their clinical, roentgenologic and pathologic appearance. The disease usually runs a chronic progressive course, with a mortality of about 50 per cent. Coccidioidal granuloma is rare, even in the San Joaquin Valley, in which it is stated that from 40 to 50 new cases per year occur.

This was the only type of human infection recognized until 1936, when Dickson [1] and Dickson and Gifford [2] demonstrated that *Coccidioides immitis* was the cause of a relatively common benign disease which had long been known locally as San Joaquin Valley fever, or "desert fever." This disease is characterized by an acute onset with fever, malaise, general aches and pains, sore throat, cough, and usually scanty sputum. The latter is sometimes blood tinged and may be copious, but it often disappears after a few days. There may be a transient erythematous eruption. At the onset the infection is often mistaken for "influenza" or a severe cold, and the symptoms are frequently so mild that the patient does not come under medical observation.

After about two weeks, and often after a partial remission, characteristically a typical erythema nodosum eruption appears over the legs, more rarely on the arms, scalp, or about the neck. This may be accompanied by a recurrence of fever, and by acute joint pains and occasionally conjunctivitis. There is often a moderate leukocytosis and an eosinophilia. The eruption gradually subsides, and complete recovery nearly always occurs. This is followed by a high degree of immunity which is probably lifelong. It has been shown that the appearance of the erythema nodosum coincides with or closely follows the development of a high degree of hypersensitiveness to the fungus. The eruption is believed to be a nonspecific allergic phenomenon analogous in its pathogenesis to the similar eruption which is often observed in cases of tuberculosis.

[1] DICKSON, E. C.: Coccidioides infection: Part I, Arch. Int. Med., 1937, lix, 1029–1044.
[2] DICKSON, E. C., and GIFFORD, M. A.: Coccidioides infection (coccidioidomycosis). II. The primary type of infection, Arch. Int. Med., 1938, lxii, 853–871.

Although this eruption has been regarded as a characteristic feature of San Joaquin Valley fever and, indeed, was almost essential for its clinical recognition, it has since been shown that many similar mild primary infections with *Coccidioides immitis* occur without the eruption. In fact, the eruption appears in only from 2 per cent to 5 per cent of the cases.

Clinically the most characteristic feature of primary coccidioidomycosis is to be found in the pulmonary lesions. Abnormalities demonstrable on physical examination are variable and often trivial, but the roentgenologic changes are usually definite and fairly characteristic. These have been described by Farness and Mills,[3] Winn,[4] and others, and in this number of the Annals of Internal Medicine Winn and Johnson report a study of the roentgenologic changes in 40 cases of primary coccidioidal infection. This study illustrates clearly the general character of the lesions and their diversity. The resemblance to early tuberculous lesions is striking. One of the most interesting features is the early appearance of small cyst-like cavities, with little evidence of reaction on the part of the surrounding tissues; the early healing in some cases; and their persistence in others, with little tendency to progress, and with negligible effect on the general health of the patient, even though organisms are excreted in abundance in the sputum.

The diagnosis depends primarily on demonstrating the organism in the sputum. This may be done by direct examination, by culture, or by animal inoculation. In the sputum (best examined in fresh moist preparations), as well as in the tissues, *Coccidioides immitis* occurs as spherical structures about 30 micra in diameter, having a thick, highly refractile cell wall. In the parasitic stage the organism reproduces by endosporulation, and the small endospores can often be seen within the spherules. There is never budding nor hypha formation. The spherules are not infectious unless actually inoculated into the tissues. On culture media (preferably Sabouraud's agar), however, hyphae grow out from these spherules, and form colonies consisting of a branching septate mycelium. Aerial hyphae grow out, and in them are produced myriads of minute chlamydospores. Local infections, however, may be acquired through skin abrasions.

The cultural and morphological characters of the organism are not entirely distinctive and positive identification requires animal inoculation, preferably intratesticular injection in guinea pigs. If either infected sputum or culture is used, after 10 days to two weeks the characteristic spherules may be formed in the tissues.

Just how and where the organism passes through this saprophytic stage under natural conditions has not been demonstrated. It has been suggested that it grows in the soil during the wet season, producing spores which are blown about in dust during the dry season. There is strong epidemiologic evidence that the infection is actually so acquired. The organism has been

[3] FARNESS, O. J., and MILLS, C. W.: Coccidioides infection, Am. Rev. Tuberc., 1939, xxxix, 266.

[4] WINN, W. A.: Pulmonary cavitation associated with coccidioidal infection, Arch. Int. Med., 1941, lxviii, 1179–1214.

isolated from the soil as well as from small wild rodents in infested regions by Emmons [5] and others. The number of successful isolations, however, was relatively so small (5 of 150) that it seems unlikely there can be any widespread multiplication of the organism in the soil.

A positive diagnosis of coccidioidal infection may also be made by intracutaneous tests with coccidioidin. This is a filtrate of a broth culture of the organism, analogous to tuberculin. The reaction usually becomes positive within 10 days or two weeks after infection and remains so for long periods of time, possibly throughout the life of the individual. Studies of selected groups of individuals living in regions in which the disease is prevalent, made by Smith [6] and others, have shown a high incidence of positive reactors. Thus, in a group of 2700 school children over half gave positive reactions. Among those who had lived in the Valley less than one year, only 17 per cent gave a positive reaction, but 77 per cent of those with a residence there of more than 10 years did so. On the other hand, half of the cases showing clinical evidence of infection had lived in the Valley less than one year, and two-thirds less than two years.

Such observations indicate that in the affected regions the bulk of the population eventually becomes infected with *Coccidioides immitis* and acquires, probably, a lasting immunity. In a large majority of cases the infection is symptomless or so nearly so that it is not recognized. Most of those who show clinical evidence of infection run a benign course and recover after a few weeks. In some cases, however, the disease may run a more severe course, sometimes simulating a severe bronchopneumonia or a chronic pulmonary tuberculosis (Farness,[7] Winn and Johnson). In only one out of several hundred cases does a general dissemination occur and the malignant form of coccidioidal granuloma develop.

The disease is not restricted to California. It is known to be prevalent in portions of Texas and Arizona, and it is probable that it will extend to other areas in the desert region, if it has not already done so. The presence of military camps in this region makes it probable that many of the men will acquire the infection and be a possible means of disseminating it widely wherever climatic conditions are such that the organism can complete the saprophytic phase of its life cycle. Thus Shelton [8] has reported that of 736 men who gave negative coccidioidin reactions on admission to Camp Roberts, 14 reacted positively when retested three months later. Manifestly, it is important that physicians generally be aware of the existence of this disease and alert to recognize it if it should appear unexpectedly in new regions.

[5] Emmons, C. W.: Isolation of coccidioides from soil and rodents, Pub. Health Rep., 1942, lvii, 109–111.

[6] Smith, C. E.: Epidemiology of acute coccidioidomycosis with erythema nodosum, Am. Jr. Pub. Health, 1940, xxx, 600–611.

[7] Farness, O. J.: Coccidioidomycosis, Jr. Am. Med. Assoc., 1941, cxvi, 1749–1752.

[8] Shelton, R. M.: A survey of coccidioidomycosis at Camp Roberts, California, Jr. Am. Med. Assoc., 1942, cxviii, 1186–1190.

REVIEWS

Synopsis of Materia Medica, Toxicology and Pharmacology. By FORREST RAMON DAVISON, B.S., M.Sc., Ph.D., M.B., Medical Department, The Upjohn Co. Kalamazoo, Mich.; formerly Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock. 2nd Ed. 695 pages; 13 × 20 cm. C. V. Mosby Co., St. Louis. 1942.

Dr. Davison's book has presented a complete summary, briefly and thoroughly, on the essential use of drugs for the student of medicine and the practicing physician. Two guiding principles developed in the first edition of this book have been followed in the second edition, namely, that pharmacology is an integral part of medicine and that the study of drugs on a theoretical basis cannot be divorced from their practical application in the treatment of disease.

The author treats the principles of pharmacology, toxicology and prescription writing. The drugs are classified and a summary of materia medica is given in Part I. In Part II the subject of pharmacology is treated from the point of view of the various systems of the body on which drugs act. To illustrate, Chapter 5 in Part II deals with the drugs acting on the skin and mucous membranes, whereas Chapter XI treats drugs acting on the central nervous system, sub-heading, cerebrospinal nervous system.

The book contains numerous illustrations which are helpful in understanding the fate and action of various pharmacological agents.

After each chapter a selected bibliography follows.

The author is to be commended for his completeness in the selection of his material which makes this book a valuable addition to any physician's library.

J. C. K., JR.

Religion in Illness and Health. By CARROLL A. WISE, Chaplain, Worcester State Hospital, Worcester, Mass. 279 pages; 14.5 × 21 cm. Harper and Bros., New York. 1942. Price, $2.50.

This book is another valuable contribution to the body of literature that has been produced in recent years and that is calculated to promote better understanding and coöperation between physician and minister for the sake of the individual person who needs their combined assistance.

The author is a minister who, as Chaplain of Worcester State Hospital, has had years of training and study that well qualify him to write a most stimulating book. He is not trying to produce a superficially "popular" treatise. Neither is he a faddist. Rather he is a scientifically trained man giving a clear and careful exposition of the basic problems of human personality and its surrounding cultures that lead to illness or health. He insists that the whole person must be studied. No adequate understanding can be reached by a diagnosis of certain faulty or unhealthy parts. Man is not a mechanism but an organism and must therefore be understood as a whole.

In this process, religion has a very important part to play. Its contribution to health is primarily preventive, and secondarily curative. Religion provides insights into the nature and meaning of life. It helps men to face the facts of experience honestly and rightly. It creates more integrated, and thus more healthy, personalities.

This is a good book. It ought to be helpful to doctors, but even more so to ministers and social workers. Like the First Aid courses given by the Red Cross, it shows some of the damage that clergymen and others can do to the health of people.

It warns them of some things not to do. But best of all, it furnishes a basis for expanding thought and deepening understanding of human beings and their needs.

T. G. S.

Wounds and Fractures. By H. WINNETT ORR, M.D., F.A.C.S. 227 pages; 16.5 × 26 cm. Charles C. Thomas, Springfield, Illinois. 1941. Price, $5.00.

The work, "Wounds and Fractures" by H. Winnett Orr, is a tribute to the surgical skill of an exceptional man, but the author fails to realize that methods which are simple to him may be impossible for others less gifted to carry out.

He emphasizes early treatment of fractures and will accept nothing but the best possible position and fixation. Good surgery is demanded as a preliminary to successful (Orr method) infrequent dressing routine. It is refreshing to find one brave enough to treat wounds without once mentioning sulfonamides, which reiterates that good surgery is still at a premium. He has given little space to wounds not associated with fractures.

The author criticizes many accepted methods without satisfactory explanation. He decries a method of pin fixation in common use, which, however, is much like his own. He speaks lightly of shock and gas bacillus infection.

Certain chapters describe his methods too briefly, but the style is graceful, making reading easy and rapid. The book will be enjoyed by all interested in this field of surgery, and many axioms will be remembered.

O. C. B.

COLLEGE NEWS NOTES

Supplementary List of Members of the American College of Physicians

On Active Military Duty

In the July, 1942, issue of this Journal there appeared a list of the members of the American College of Physicians who up to that time were known to be on active military duty. Since that time we have had reports that the following Fellows and Associates have been called to active duty with the armed forces of their country:

Maurice J. Abrams
Jacques H. Ahronheim
William W. Alexander
Edgar V. Allen
Frank J. Altschul
Charles H. Armentrout
Dudley C. Ashton
Harold C. Atkinson

James P. Baker
Gordon W. Balyeat
Joseph Bank
Walter Bauer
Abraham Becker
Julien E. Benjamin
Clifton H. Berlinghof
Michael Bevilacqua
Earl J. Bieri
Samuel Blackwell
Franklin B. Bogart
Francis J. Braceland
Charles A. Breck
Hugh R. Butt
Charles S. Byron

John W. G. Caldwell
Donald C. Campbell
Louie T. Carl
Henry R. Carstens
Charles R. Castlen
William Chester
H. Dumont Clark
Thomas A. Clawson, Jr.
James H. Closson
Charles B. Coggin
Leon H. Collins, Jr.
Ralph R. Cooper
Darrell C. Crain
George W. Cramp
Robert W. Currie
John K. Curtis
Edward H. Cushing
Haydn H. Cutler

Alva D. Daughton
Marion T. Davidson
Edward A. Delarue, Jr.
Douglas Donald
Charles D. Driscoll

Harold K. Eynon

Theodore R. Failmezger
Waldo B. Farnum
Elliston Farrell
Dan W. Fisher
Donald E. Forster
Marshall N. Fulton

Stanley M. Goldhamer
Henry B. Gotten
Stephen A. Graczyk
Robert W. Graham

Frank W. Halpin
George C. Hamilton
John R. Hamilton
M. Coleman Harris
Meyer M. Harrison
Andrew D. Hart, Jr.
Thomas N. Horan
Arthur J. Horton
George H. Houck
Albert S. Hyman

Irving R. Juster

Mennasch Kalkstein
John L. Kantor
T. Douglas Kendrick
Francis E. Kenny
Otis G. King
J. Murray Kinsman

Michael Lake
John E. Leach
Edward P. Leeper
Charles E. Lemmon

Jerome S. Levy
Bernard I. Lidman
McKinley London
William S. Love, Jr.

Thomas T. Mackie
Emory H. Main
Orlando B. Mayer
Jesse McCall
Harold P. McGan
Perry J. Melnick
Ralph W. Mendelson
Harold R. Merwarth
James C. Metts
Frank Meyers
Solomon G. Meyers
Earl L. Mills
Morris E. Missal
Matthew Molitch
Bert E. Mulvey
John M. Murphy

Bergein M. Overholt
Sam A. Overstreet

Thomas H. Pargen
Frazier J. Payton
Abraham Penner
Frank S. Perkin
Evans W. Pernokis
Elbert L. Persons
Kenneth Phillips
Morton M. Pinckney
Herbert Pollack
Alvin E. Price

Jack O. W. Rash
Joseph W. Rastetter
Walter G. Reddick
Arthur J. Revell
Stephen Reynolds
Rafael Rodriguez-Molina
Paul B. Roen
Jack Rom
Thomas L. Ross, Jr.
Chauncey L. Royster
Hendrik M. Rozendaal

Henry A. Schroeder
Leon Schwartz
Maurice M. Scurry
Loyd W. Sheckles, Jr.
Karl Shepard
Euclid M. Smith
Wilson F. Smith
Edward D. Spalding
Gilbert M. Stevenson
Lewis T. Stoneburner, III

Elam C. Toone, Jr.
James H. Townsend
Woodford B. Troutman
Pat A. Tuckwiller
Arthur R. Twiss

William G. Ure

John Vaughn

Emmett D. Wall
James A. Walsh
Charles H. Watkins
* Roger Sherman Whitney
Carl J. W. Wilen
James N. Williams
Francis C. Wood
Raymond J. Wyrens

Richard H. Young

* British Red Cross.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. W. A. D. Anderson (Associate), St. Louis, Mo.—"Synopsis of Pathology";
Frederick Ceres, F.A.C.P., Captain, (MC), U. S. Navy—"Aviation Medicine Technicians' Manual";
Dr. Irvine H. Page (Associate), Indianapolis, Ind.—"Chemistry of the Brain."

Reprints

Dr. Orville E. Egbert, F.A.C.P., El Paso, Tex.—1 reprint;
Dr. J. William Finch, F.A.C.P., Hobart, Okla.—1 reprint;

Dr. Clifton Keck Himmelsbach, F.A.C.P., Lexington, Ky.—2 reprints;
Dr. Raymond Hussey, F.A.C.P., Baltimore, Md.—2 reprints;
Dr. Richard DeMonbrun Kepner, F.A.C.P., Honolulu, T. H.—2 reprints;
Dr. W. W. Klement (Associate), Cincinnati, Ohio—1 reprint;
Dr. James R. Lisa, F.A.C.P., New York, N. Y.—15 reprints;
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint;
Dr. Emilie V. Rundlett, F.A.C.P., Jersey City, N. J.—1 reprint;
Dr. John H. Shaffer, F.A.C.P., Detroit, Mich.—1 reprint;
Dr. Hugh Stalker, F.A.C.P., Detroit, Mich.—3 reprints;
Ralph M. Thompson, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint;
Dr. Stuart L. Vaughan, F.A.C.P., Buffalo, N. Y.—1 reprint;
Leon H. Warren (Associate), Major, (MC), U. S. Army—12 reprints;
Dr. John W. Williams, F.A.C.P., Cambridge, Mass.—32 reprints.

Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J., has donated a personally executed photograph entitled "Grand Central" to the College Headquarters. This work was exhibited at the recent meeting of the American Physicians' Art Association.

Schedule of Examinations by Certifying Boards

The following Boards have announced schedules of their examinations as follows:

American Board of Internal Medicine: William A. Werrell, M.D., Assistant Secretary 1301 University Ave. Madison, Wis.	*Written Examinations:* Will be given in various centers October 19, 1942. Applications must be filed before September 1, 1942. *Oral Examinations:* Philadelphia, Pa., April, 1943, in advance of the meeting of the American College of Physicians; San Francisco, Calif., 1943, in advance of the meeting of the American Medical Association.
American Board of Dermatology and Syphilology: C. Guy Lane, M.D., Secretary 416 Marlboro St. Boston, Mass.	*Written Examinations:* Will be given in various centers, October 12, 1942. *Oral Examinations:* Chicago, Ill., December 4–5, 1942.
American Board of Pathology: F. W. Hartman, M.D., Secretary Henry Ford Hospital Detroit, Mich.	*Written and Oral Examinations:* Richmond, Va., November 9–10, 1942.
American Board of Pediatrics: C. A. Aldrich, M.D., Secretary 707 Fullerton Ave. Chicago, Ill.	*Oral Examinations:* Chicago, Ill., November 1–3, 1942, in advance of the meeting of the American Academy of Pediatrics; New York, N. Y., December 4–6, 1942.
American Board of Psychiatry and Neurology: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N. W. Washington, D. C.	*Oral Examinations:* New York, N. Y., December, 1942; San Francisco, Calif., June, 1943.

AMERICAN BOARD OF RADIOLOGY:
B. R. Kirklin, M.D., Secretary
Mayo Clinic
Rochester, Minn.

Oral Examinations: Chicago, Ill., November 27–29, 1942.

For further details and application forms communicate with the respective secretaries.

ACTING GOVERNORS OF THE COLLEGE APPOINTED FOR MINNESOTA AND EASTERN PENNSYLVANIA

Dr. Edgar V. Allen, Rochester, Minn., College Governor for that State, has, as of August 1, entered the Medical Corps of the U. S. Army as a Lieutenant Colonel, as Consultant in Medicine and Coördinator of Professional Service for the 7th Corps Area. Dr. E. H. Rynearson of Rochester, Minn., has been appointed Acting Governor for Minnesota to serve until such time as Governor Allen may return.

As of August 1, Dr. Edward L. Bortz, Philadelphia, Governor for Eastern Pennsylvania, who is a Lieutenant Commander in the Medical Corps of the U. S. Navy, has been transferred from the Philadelphia Naval Hospital, and Dr. Thomas M. McMillan, 2044 Locust Street, Philadelphia, has been appointed Acting Governor by the Executive Committee of the College. Dr. McMillan will serve during Dr. Bortz's absence.

Dr. LeRoy H. Sloan, F.A.C.P., College Governor for Northern Illinois, has been elected President of the Chicago Society of Internal Medicine. Dr. Italo Volini, F.A.C.P., was elected Vice President, and Dr. Richard Capps (Associate), was elected Secretary. Dr. Capps is now on active military duty with the Northwestern University Unit, and during his absence Dr. Howard Alt will act as Secretary Pro Tem.

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., has been appointed Consultant in Medicine to the Griffin Hospital, Derby, Conn.

Dr. Robert H. Felix, F.A.C.P., U. S. Public Health Service, has been assigned to the U. S. Coast Guard Academy, New London, Conn., which is a training school for officers of the Coast Guard. Dr. Felix will be in charge of organizing, developing, and administering a psychiatric service for the cadets at the Academy.

Dr. Charles G. Sinclair, F.A.C.P., has been advanced from Lieutenant Colonel to Colonel in the Medical Corps of the U. S. Army, and has been assigned as Camp Surgeon and Commanding Officer of the Station Hospital, Camp Hood, Tex.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, was awarded the blue ribbon and collar of the Order of Merit, Grade of Commander, by the Government of the Republic of Chile, for "excellence of administration and research in solving public health problems."

The Alumnae Association of the Woman's Medical College of Pennsylvania, Philadelphia, held its 67th Annual Meeting, June 2, 1942. At a scientific session of this meeting, Dr. Mary M. Spears, F.A.C.P., Philadelphia, Pa., spoke on "Diagnosis of Lesions of Lower Colon," and Dr. Frieda Baumann, F.A.C.P., Philadelphia, Pa., spoke on "The Clinical Aspects of the Sulfa Drugs." Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J., Acting President of the College, presented a report of the Board of Corporators to the Association.

At a recent meeting of the Arizona State Medical Association in Prescott, Dr. Virgil G. Presson, F.A.C.P., Tucson, was chosen Vice President and Dr. William W. Watkins, F.A.C.P., Phoenix, was reëlected Secretary.

Dr. Percy T. Magan, F.A.C.P., has retired as President and Professor of Medical Ethics at the College of Medical Evangelists, Los Angeles, Calif. Dr. Magan was the guest of honor at a reception in Los Angeles, May 13, held by students, alumni, and friends to mark his retirement as President of the College.

Dr. Walter E. Macpherson (Associate), Los Angeles, Calif., Professor of Internal Medicine and Physiology at the College, has been named President succeeding Dr. Magan.

Dr. Josiah J. Moore, F.A.C.P., Chicago, Ill., has been elected President of the Society of Illinois Bacteriologists.

Dr. Stanley G. Wolfe, F.A.C.P., Shreveport, was installed as President of the Louisiana State Pediatric Society at its recent meeting.

Dr. Kennon Dunham, F.A.C.P., Cincinnati, was reëlected President of the Ohio Public Health Association at its annual meeting in Columbus, May 21, 1942.

Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y.. spoke on "Important Medical Measures in the Management of Gastrointestinal Diseases" at a joint meeting of the Third and Twelfth Councilor Districts of the Medical Society of the State of Pennsylvania in Sayre, June 24.

Dr. Baldwin L. Keyes, F.A.C.P., has been named Professor of Psychiatry; Dr. Martin E. Rehfuss, F.A.C.P., Sutherland M. Prevost Lecturer in Therapeutics in the Department of Medicine; Dr. Garfield G. Duncan, Clinical Professor of Medicine at the Jefferson Medical College of Philadelphia.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., has been elected President of the American Therapeutic Society, and Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C., has been reëlected Secretary.

Dr. Eugene M. Landis, F.A.C.P., Charlottesville, Va., has been elected President of the American Society for Clinical Investigation, and Dr. Wesley W. Spink, F.A.C.P., Minneapolis, Minn., Secretary.

Dr. James E. Paullin, F.A.C.P., Atlanta, Ga., President of the College, was honored at a dinner, July 7, given by the Fulton County (Ga.) Medical Society to mark his election as President-Elect of the American Medical Association.

Dr. Harold C. Ochsner, F.A.C.P., Indianapolis, has been named Secretary-Treasurer of the Indiana Roentgen Society.

Dr. William Dameshek, F.A.C.P., has been appointed Professor of Clinical Medicine at Tufts College Medical School, Boston, Mass.

Dr. Roger I. Lee, F.A.C.P., Boston, Mass., was chosen President-Elect of the Massachusetts Medical Society at its annual meeting in Boston, May 25, 1942.

Dr. Franklin H. Top (Associate), has been named Medical Director of the Herman Kiefer Hospital, Detroit, Mich.

Dr. Thomas A. Lebbetter, F.A.C.P., Yarmouth, Nova Scotia, a Lieutenant Colonel in the Medical Corps of the Royal Canadian Army, is now attached to Army Headquarters at Ottawa as Assistant Adjutant General.

At the annual meeting of the North Dakota State Medical Association in Jamestown, May 18–20, 1942, Dr. Gordon R. Kamman, F.A.C.P., St. Paul, Minn., spoke on "The Depressed Patient," and Dr. Arthur C. Fortney, F.A.C.P., Fargo, N. D., and Dr. Paul J. Breslich, F.A.C.P., Minot, N. D., were among those who conducted a symposium on "Encephalomyelitis."

At the annual meeting of the Texas State Heart Association in Houston, May 11, Dr. Marvin L. Graves, F.A.C.P., Houston, was elected President, Dr. Merritt B. Whitten (Associate), Dallas, Vice President, and Dr. Walter B. Whiting, F.A.C.P., Wichita Falls, Secretary-Treasurer.

Dr. Roy L. Leak, F.A.C.P., Middletown, has been named President of the Connecticut State Medical Society.

At the recent annual meeting of the Radiological Society of New Jersey, Dr. Harry J. Perlberg, F.A.C.P., Jersey City, was named Secretary.

Dr. Roy R. Snowden, F.A.C.P., College Governor for Western Pennsylvania, Pittsburgh, spoke on "Recent Advances in Our Knowledge of Hypertension" at a meeting of the Eighth Councilor District of the Medical Society of the State of Pennsylvania in Conneaut Lake, July 15.

Dr. Daniel P. Griffin, F.A.C.P., Bridgeport, was elected President of the Connecticut Society for Psychiatry and Neurology at its recent annual meeting.

Dr. Paul P. McCain, F.A.C.P., Superintendent of the North Carolina Sanatorium for the Treatment of Tuberculosis at Sanatorium and the Western North Carolina Sanatorium at Black Mountain, has been named Superintendent of the Eastern North Carolina Sanatorium now under construction in Wilson.

Dr. David W. Baird, F.A.C.P., Associate Dean and Associate Clinical Professor of Medicine at the University of Oregon Medical School, Portland, has been appointed Acting Dean of the Medical School.

Among the speakers at a meeting of the Fifth Councilor District of the Medical Society of the State of Pennsylvania, July 9, in Harrisburg, were:

Dr. Harry B. Thomas, F.A.C.P., York—"Practical Problems in Diabetes";

Charles R. Reynolds, F.A.C.P., Major General, (MC), U. S. Army (Retired)—"Tuberculosis in the War";
Dr. Edward L. Bortz, F.A.C.P., Philadelphia—"New Light on Old Folks."

At a meeting of the North Texas Medical Association in Terrell, June 2, Dr. George R. Herrmann, F.A.C.P., Galveston, spoke on "Interpretation of Electrocardiogram and Coronary Artery Disease," and Dr. Milford O. Rouse, F.A.C.P., Dallas, spoke on "Diagnosis and Medical Management of the Gallbladder."

The American Dietetic Association will hold its twenty-fifth annual meeting at the Hotel Statler in Detroit on October 19 to 22.

Tuberculosis Increases in Great Britain

Recent announcements by William H. Stoneman of the Medical Research Council indicates a sharp rise in the incidence of tuberculosis in Great Britain, with an increase in deaths from both pulmonary and nonpulmonary types since the beginning of the war. Between 1939 and 1940 deaths from pulmonary tuberculosis increased 6 per cent and in 1941 there was an additional 10 per cent increase over 1939. Even a greater increase in the percentage of deaths from nonpulmonary tuberculosis occurred. There was a 40 per cent increase between 1939 and 1941 in deaths from tuberculosis meningitis. The increase in the tuberculosis death rate, except for the increase of 34 per cent between 1939 and 1941 in venereal diseases, is the most significant threat in the wartime health situation of England.

Various causes have been advanced such as the increased use of unpasteurized milk; the closing of sanatoria, releasing carriers; a general decrease in physical resistance due to long working hours and unsatisfactory diet; the difficulty in providing regular treatment because of the shifting of infected people who are still working; increased numbers of contacts with active carriers; and lack of facilities for proper treatment.

It has been pointed out that thus far there have been no widespread epidemic diseases as had been expected, and furthermore, that in the case of some diseases, which were expected greatly to increase during the war, there has actually been a marked decrease, both in incidence and in percentage of fatal cases.

F.A.C.P.'s Become Officers, Montana State Medical Association

At the 64th Annual Meeting of the Montana State Medical Association in Missoula, Mont., July 8–10, 1942, Dr. Ernest D. Hitchcock, F.A.C.P., College Governor for Montana, of Great Falls, was inducted as President; Dr. J. P. Ritchey, F.A.C.P., Missoula, was elected President-Elect; and Dr. Thomas F. Walker, F.A.C.P., Great Falls, was elected Secretary.

Dr. Walter L. Nalls, F.A.C.P., Richmond, was recently elected Secretary-Treasurer of the Society of Chest Physicians of Virginia.

Mississippi Valley Medical Society to Meet in Quincy, Illinois, September 30–October 2

The 8th Annual Meeting of the Mississippi Valley Medical Society, under the Presidency of Dr. Dan G. Stine, F.A.C.P., Columbia, Mo., will be held at the Hotel

Lincoln-Douglas, Quincy, Ill., September 30–October 2, 1942. About twenty-five clinician-teachers will present a program of lectures, demonstrations, and instructional courses.

On September 30 the courses will be given by a group of Kansas City, Mo., and Rochester, Minn., clinicians, among whom are Dr. Graham Asher, F.A.C.P., Kansas City, on "Clinical Factors Which Influence Digitalis Administration" and Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn., on "Insulin in the Treatment of Diabetes" and "Food Control for Public Health: Nutritional Considerations." On October 1 Chicago clinicians will be in charge, among whom will appear Dr. Robert A. Black, F.A.C.P., on the subject of "Rheumatic Heart Disease in Children." For October 2 the following are among those on the program: Dr. James H. Hutton, F.A.C.P., Chicago, on "Endocrine Diagnosis and Treatment from the Clinician's Standpoint" and Dr. Arthur L. Smith, F.A.C.P., Lincoln, Nebr., on "Treatment of Heart Emergencies with Reproduced Heart Sounds."

Medical Editors to Meet at Quincy, Ill., September 30

The 2nd Annual Meeting of the Mississippi Valley Medical Editors' Association will be held at the Hotel Lincoln-Douglas, Quincy, Ill., Wednesday, September 30. This will be a dinner meeting under the leadership of Dr. Clyde P. Dyer, of St. Louis, Editor of the St. Louis County Medical Bulletin and President of the Association. The meeting is being held during the 8th Annual Meeting of the Mississippi Valley Medical Society, which will also meet at the Hotel Lincoln-Douglas, September 30, October 1, 2. All past and present medical editors and those interested in medical journalism or writing are cordially invited to attend. There is no registration fee. Program of the meeting or dinner reservations may be secured through Harold Swanberg, M.D., F.A.C.P., Secretary of the Association, W. C. U. Building, Quincy, Ill.

The Health Supplies Branch of the War Production Board has again called attention to the fact that all stocks of Quinine and Totaquine, no matter how small, have been subject to the restrictions of Conservation Order M-131 since June 19, 1942. These products may not be sold for any purpose except as an anti-malarial agent. The order extends to powder, capsules, solutions, pills and tablets and to Quinine or Totaquine stocks of all other descriptions whether or not packages have been opened.

The same restrictions apply to Cinchonine, Cinchonidine and Quinidine, except that Quinidine may be sold for the treatment of cardiac disorders. These restrictions are necessary because these drugs are urgently needed for military use. Supplies are limited since the raw material, cinchona bark, comes in most part from Java. The restrictions extend not only to the sale of these products by retail druggists but to dispensing of these drugs on physicians' prescriptions.

Calendar of Postgraduate Courses Available at Tufts Medical School

Boston, Mass.

During 1942–43

The following courses are designed for the busy general practitioner who wishes to bring his knowledge up to date. The courses are all under the auspices of Tufts Medical School, and will largely be given in the New England Medical Center (Boston Dispensary, Joseph H. Pratt Diagnostic Hospital, Boston Floating Hospital and Tufts Medical School).

Admission: Graduates of approved medical schools are eligible. They should submit evidence of membership in their State medical societies. Applications should be made to the Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston, Mass.

Fees: In addition to the tuition fees indicated, a $5.00 registration fee shall be paid, which covers any courses taken at this institution within a twelve-month period.

Electrocardiography

September 28–October 2, 1942; also, May 10–14, 1943.

Fee, $25.00.

Demonstrations and intensive study of records, present status of electrocardiogram interpretation in coronary disease; arrhythmias, syphilitic, congenital and rheumatic heart disease; myxedema, pericarditis, etc. Drs. Heinz Magendantz, Samuel Proger and Associates.

Internal Medicine

October 5–30, 1942; also, May 3–28, 1943.

Fee, $50.00.

Ward rounds and staff conferences in the Joseph H. Pratt Diagnostic Hospital, examination of patients in the different medical clinics of the Boston Dispensary; informal discussions with chief technicians of pathology, bacteriology and chemistry laboratories, followed by lectures by physicians on their various specialties, such as hematology, neurology, gynecology, allergy, cardiology, endocrinology, nephritis and hypertension, spleen and liver diseases, etc. Dr. Samuel Proger in charge.

Endocrinology

November 9–13, 1942; also, May 24–28, 1943.

Fee, $25.00.

A course intended to clarify more recent advances in this field, stressing their clinical application; demonstrations of tests and laboratory methods, attendance at the Boston Dispensary Endocrine Clinics, lectures and conferences, ward rounds and examination of patients. Dr. Charles H. Lawrence in charge.

Hematology A

November 16–21, 1942.

Fee, $25.00.

Conferences and laboratory and clinical work at Pratt Diagnostic Hospital and Boston Dispensary; case presentations and lectures on bone marrow, anemia, leukopenic disorders, leukemia, bone marrow biopsy, etc. Drs. Heinrich Brugsch and William Dameshek.

Cardiology

November 16–21, 1942; also, May 3–8, 1943.

Fee, $25.00.

Practical application of present-day knowledge of heart disease; therapy of heart disorders; daily lectures followed by pathological demonstrations and case presentations. Dr. Samuel Proger in charge.

Pediatrics

January 4–30, 1943.

Fee, $50.00.

Daily ward rounds in the Boston Floating Hospital and examination of patients on the wards of the Floating Hospital and in the Children's Clinics of the Boston Dispensary. Afternoon visits to South Department of the Boston City Hospital, the Diabetes Clinic of the New England Deaconess Hospital, the Evangeline Booth Hospital and the Chapin Hospital in Providence, R. I., where contagious diseases, diseases of the newborn, prematurity and diabetes will be taken up. Enrollment limited to four. Dr. James Marvin Baty in charge.

Radiology

January 12–15, 1943.

Fee, $25.00.

General practitioner's course; x-ray interpretation in diseases of the heart, gastrointestinal tract and bone, in obstetrical cases, and in diseases of children. Dr. Alice Ettinger in charge.

Dermatology B

January 18–23, 1943.

Fee, $25.00.

Mornings at the Skin Clinic of the Boston City Hospital and in the Syphilis Clinic; afternoon lectures, demonstrations and discussions. Dr. William P. Boardman in charge.

Diabetes

January 18–23, 1943.

Fee, $25.00.

A study of the clinical methods and procedures most effective in the diagnosis and treatment of diabetes mellitus and its complications. Dr. Joseph Rosenthal in charge.

Advanced Electrocardiography

January 25–27, 1943.

Fee, $20.00.

A three-day continuation course planned especially for those who have taken the preliminary course, or who have had sufficient experience in the interpretation of electrocardiograms. Dr. Heinz Magendantz in charge.

Gastro-Enterology

February 8–13, 1943.

Fee, $25.00.

Review of modern methods, their importance in diagnosis and treatment and their limitations; systematic discussion of diagnosis, treatment and complications of the commoner gastro-intestinal diseases. Dr. Katherine S. Andrews in charge.

Dermatology A

May 17–22, 1943.

Fee, $25.00.

A highly concentrated course discussing from the practical standpoint the diagnosis and therapy of the commoner diseases of the skin. Dr. Francis M. Thurmon in charge.

Allergy

October 19–23, 1942, and May 17–21, 1943.

Fee, $25.00.

Present-day status of the diagnosis and treatment of allergic conditions; lectures on hayfever, bronchial asthma, atopic eczema, urticaria, serum disease, histamine and the pharmacology of allergic diseases; clinic demonstrations at Boston Dispensary. Dr. Ethan Allan Brown in charge.

Hematology C

July 5–17, 1943.

Fee, $75.00.

An intensive course; lectures, informal discussions, laboratory and bedside teaching. Dr. William Dameshek in charge.

OBITUARIES

DR. WILLIAM McCULLY JAMES

Dr. William McCully James, former Governor of the College, died of a cerebral hemorrhage on July 10, 1942, at the age of 62 years, at the Panama Hospital.

Dr. James was born May 29, 1880, at Richmond, Virginia. He took his premedical training at Johns Hopkins University, and graduated in Medicine from the Medical Department of the University of Virginia, in 1906. He came to the Isthmus immediately after graduation, and interned at Colon Hospital, later serving at Ancon (now Gorgas) Hospital, where he was assistant to the Chief of the Medical Service from 1910 to 1914, and then as District Physician at Ancon, Canal Zone. He left the Government service in 1916 to join with Dr. A. B. Herrick and Dr. D. F. Reeder in establishing the Panama Hospital and Herrick Clinic, of which he was Chief of the Medical Service until his death. During the first World War, he served as a Major in the Medical Corps of the United States Army, and was later commissioned a Lieutenant-Colonel in the Medical Reserve Corps. He was a Colonel in the Panamanian Army during the border dispute with Costa Rica in 1921. He was for many years Consultant in Tropical Medicine to the United Fruit Company.

He was always an ardent and untiring student, and soon became recognized as an authority on tropical diseases, especially malaria and amebiasis, on which he published numerous papers, including a monograph on the Etiology and Treatment of Hemoglobinuric Fever in the Canal Zone, written in collaboration with Dr. W. E. Deeks, and published by the Department of Sanitation of the Isthmian Canal Commission; and a monograph on a Study of the Entamoebae of Man in the Panama Canal Zone, published in the Annals of Tropical Medicine and Parasitology (Liverpool). In 1912, he prepared an exhibit on malaria and dysentery for the Department of Sanitation of the Isthmian Canal Commission, which was awarded a Certificate of Honor at the Atlantic City Convention of the American Medical Association. An exhibit on amebiasis, prepared in collaboration with Drs. L. B. Bates, Lawrence Getz, and J. J. Vallarino, was awarded a Bronze Medal at the Washington Convention in 1927; and in 1934, at the Cleveland Convention, with Drs. Bates, Getz, and Icaza, he was awarded the Class II Gold Medal for a complete and detailed exhibit on the pathology of amebiasis.

He was a fellow of the American Medical Association and Southern Medical Association, a charter member and eighth president of the Medical Association of the Isthmian Canal Zone, a charter member and past first vice president of the National Medical Association of Panama, a charter member of the American Society of Tropical Medicine, a member of the American Society of Parasitologists, an honorary member of the National

Gastro-enterological Association, a fellow of the Royal Society of Tropical Medicine and Hygiene, and of the Royal Microscopical Society, an associate member of the Medical and Surgical Society of Guayaquil, Ecuador, an honorary member of the Rafael Calvo Society of Cartagena, Colombia, and a Diplomate of the American Board of Internal Medicine. He was a Fellow of the American College of Physicians since 1926, and Governor for Panama and the Canal Zone from 1928 to 1941.

He was a member of Kappa Alpha and Phi Rho Sigma fraternities, and of Phi Beta Kappa and Alpha Omega Alpha honorary fraternities; a thirty-third degree Mason, member of the Scottish and York Rite Bodies, and Noble of the Mystic Shrine. He was for many years, a member of the Cosmos Club, of Washington, and of the Union Club and Golf Club, of Panama. He was a founder and past president of the American Society of Panama, and a member of the American Legion and Rotary Club. The Republic of Ecuador decorted him with the Order of Merit, and the Republic of Panama with the Order of Vasco Nuñez de Balboa.

Dr. James' death was a great loss to the Isthmian community, and to the medical profession. He was an eminent physician, whose ability, sympathetic understanding, and great personal interest in all his patients, won him thousands of devoted friends, from all parts of the Isthmus and Central America. He did much to promote friendship and understanding between the American and Panamanian communities. He was honest, loyal, unselfish, and deeply devoted to his profession. He had an outstanding personality, and was an important part of Isthmian life. Panama and the Canal Zone will not be the same without "Dr. James."

He is survived by his wife, Mrs. Mary James, a daughter, Mary Celeste, and a brother, Alfred.

GILBERT M. STEVENSON, M.D., F.A.C.P.,
Governor for Panama and the Canal Zone

DR. LOUISE TAYLER JONES

It is with a deep sense of sorrow and a keen feeling of personal loss that we record the death on December 21, 1941, of Dr. Louise Tayler Jones.

She lived a full life and her talent was often devoted to the service of people in distant lands.

In her later years it was our good fortune to have her live among us and to enrich our meetings by her presence. To recount the details of her life, to list the numerous honors that came to her, do not portray the character and the charm of personality of this distinguished woman and physician.

Born in Youngstown, Ohio, November 14, 1870, she received her A.B. degree from Wellesley College and an M.S. from George Washington University. In 1903 she graduated in Medicine from the then young Johns Hopkins University School of Medicine, and, following this, interned at the Babies' Hospital in New York. During 1907 and 1908 she was acting phy-

sician in charge at this Hospital. Following this she located in Washington and there devoted much of her time and energy to welfare work. During her years in Washington she served as Pediatrician to the Florence Crittenden Home and to the Columbia Hospital. She was an Associate at the Children's Hospital and Chief of the Child Welfare Clinic.

Her services during the first World War were outstanding. During 1915 she was Director of the American Red Cross in Serbia, and during 1919 she served with the Wellesley and American Women's Hospital Units in France.

Dr. Jones was a member of the District of Columbia Medical Society, serving a term as Vice-President. She was also a member of the Women's Medical Society of the District of Columbia; the American Academy of Pediatrics; the Medical Women's National Association, of which she was President from 1928 to 1929. She was Vice-President of the Medical Women's International Association from 1929 to 1934, and President of the Washington Branch of the American Association of University Women from 1923 to 1924. She was a member of the American Medical Association, and a Fellow of the American College of Physicians since 1926.

We of her adopted State look upon this list of honorable achievements as a fitting symbol of her worth, and we remember them with pride; but we remember her not only as an accomplished physician but also as a very gracious woman.

WALTER B. MARTIN, M.D., F.A.C.P.,
Governor for Virginia

DR. GEORGE FORBES

Dr. George Forbes was born in Brooklyn, N. Y., on November 5, 1867, and died at his home on June 23, 1942, of cancer of the colon. He received his M.D. degree from New York University Medical College in 1890. His early medical career was devoted to general practice. In 1898 he became interested in x-ray work and gradually gave more of his time to this specialty until 1915 when he limited his practice to roentgenology.

Dr. Forbes was Director of Roentgenology at St. Johns Hospital, Long Island City, 1904 to 1939; St. Catherine's Hospital, Brooklyn, 1914 to 1936; Roosevelt Hospital, New York City, 1916 to 1923; Wyckoff Heights and Bethany Deaconess Hospitals, Brooklyn, 1917 until his death.

He became a Fellow of the American College of Physicians in 1920. He was a charter member of the Radiological Society of North America, and a member of the Kings County Medical Society and the American Medical Association.

On April 10, 1940, over 400 of his friends, colleagues and former patients gave him a testimonial dinner at Essex House in New York City to honor him on the completion of fifty years of practice.

Dr. Forbest leaves a widow, the former Norene Cadmus, to whom he was married in 1891, one son, three daughters and seven grandchildren.

DR. PERCIVAL GORDON WHITE

With the untimely passing of Dr. Percival Gordon White in Los Angeles on April 28, another breach has been made in the ranks of medical men of the old school. Dr. White was a man to whom the honest practice of medicine was the most important thing in life. He never spared himself at the expense of any patient, rich or poor, and in fact he well might be alive today had he given more consideration to his own health and less to that of others, following his first coronary attack.

The son of a Lieutenant-Colonel in the British army, Dr. White was born in Woodstock, Ontario. He received his earlier education at the Woodstock Collegiate School and his medical degree from McGill University Faculty of Medicine, Montreal. He came to Los Angeles in 1910 and after the first World War broke out went overseas as a Major in the U. S. Army Medical Corps and was in charge of an evacuation hospital in France for a year. On his return to Los Angeles he renewed his former association with Dr. M. L. Moore and Dr. E. C. Moore, a partnership which later resulted in the foundation of the well-known Moore-White Clinic, in the work of which Dr. White was active until his final illness. He was a member of county and state societies, a Fellow of the American Medical Association and a Fellow of the American College of Physicians.

Dr. White was a man who stood very high in the profession. He possessed unmistakably those qualities which are the natural inheritance of the born doctor. The human element never was missing in his contact with his patients, and this, coupled with his fine medical ability, his humor, and his kindliness in his personal relations made of him a man esteemed for himself and highly respected for his professional skill. The medical profession could well do with more men of the calibre of Dr. Percy White.

Dr. White is survived by his widow, Jessie R. White, a brother and sister in Canada and hundreds of friends by whom his name will not be forgotten.

Roy E. Thomas, M.D., F.A.C.P.,
Governor for Southern California

DR. HAROLD G. F. EDWARDS

Dr. Harold G. F. Edwards was born in Abbeville, Louisiana, November 18, 1888. He received his primary education in the public schools of Abbeville, his premedical education in Jefferson College at Convent, Louisiana, and received an M.D. degree from Tulane University in 1911. Prior to his entering Tulane University he was for a time editor of the Abbeville *Herald*. After practicing medicine in Abbeville for several years, Dr. Edwards enlisted in the United States Army Medical Corps in 1917, in which he attained the rank of captain before his honorable discharge in 1919.

Following his discharge from the Army Dr. Edwards received postgraduate training in radiology at Bellevue Hospital, New York, and Cook

County Hospital in Chicago. He served as radiologist in the St. John's Hospital, Lafayette, Louisiana, from 1922 to 1928. In 1928 he removed to Shreveport, Louisiana, where he practiced radiology until his death. He was radiologist to the Willis Knighton Clinic and the Tri-State Hospital from 1930 to 1931; Director of the Tumor Clinic, Shreveport Charity Hospital, from 1932 to 1940, and Director of the X-ray Department, Shreveport Charity Hospital, from 1935 to 1940.

He held membership in the Radiological Society of North America, the American Radium Society, and the American College of Radiology. He had been President of the Third District Medical Society of Louisiana, and Secretary and later President of the Louisiana State Radiological Society. He became a Fellow of the American College of Physicians in 1929.

Dr. Edwards' principal interests and principal contributions to medical science were in the field of x-ray and radium therapy. Throughout the South he was recognized as an authority on these subjects, and made numerous contributions to the literature.

Dr. Edwards died May 2, 1942, of coronary occlusion.

EDGAR HULL, M.D., F.A.C.P.,
Governor for Louisiana

MINUTES OF THE BOARD OF GOVERNORS

ST. PAUL, MINN.

April 20, 1942

The first meeting of the Board of Governors, in conjunction with the Twenty-sixth Annual Session of the American College of Physicians, convened in the Municipal Auditorium, St. Paul, Minn., Monday, April 20, 1942, at 5 p.m., Chairman Charles H. Cocke presiding and Executive Secretary E. R. Loveland acting as Secretary.

Secretary Loveland called the roll and the following responded. (Those marked with an asterisk were alternate Governors serving in the place of the regular Governors who were absent.)

Oliver C. Melson	ARKANSAS
Fred M. Smith	IOWA
*Edgar Hull	LOUISIANA
Henry R. Carstens	MICHIGAN
Edgar V. Allen	MINNESOTA
A. Comingo Griffith	MISSOURI
*Harry T. French	NEW HAMPSHIRE
George H. Lathrope	NEW JERSEY
Charles H. Cocke	NORTH CAROLINA
*L. H. Fredericks	NORTH DAKOTA
Alexander M. Burgess	RHODE ISLAND
*L. E. Madden	SOUTH CAROLINA
Paul K. French	VERMONT
Walter B. Martin	VIRGINIA
*E. G. Bannick	WASHINGTON
Albert H. Hoge	WEST VIRGINIA
*J. H. Watkins	ALABAMA
Lewis B. Flinn	DELAWARE
Turner Z. Cason	FLORIDA
LeRoy H. Sloan	NORTHERN ILLINOIS
C. W. Dowden	KENTUCKY
Eugene H. Drake	MAINE
Louis Krause	MARYLAND
John G. Archer	MISSISSIPPI
Ernest D. Hitchcock	MONTANA
*Irving S. Wright	EASTERN NEW YORK
A. B. Brower	OHIO
Homer P. Rush	OREGON
M. D. Levy	TEXAS
Elmer L. Sevringhaus	WISCONSIN
Ramon M. Suarez	PUERTO RICO
George F. Strong	ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN
Roy E. Thomas	SOUTHERN CALIFORNIA
James J. Waring	COLORADO
*J. S. Nickum	CONNECTICUT
Wallace M. Yater	DISTRICT OF COLUMBIA
Cecil M. Jack	SOUTHERN ILLINOIS
Robert M. Moore	INDIANA

Harold H. Jones	KANSAS
Warren Thompson	NEBRASKA
Nelson G. Russell, Sr.	WESTERN NEW YORK
Leander A. Riely	OKLAHOMA
Edward L. Bortz	EASTERN PENNSYLVANIA
*L. D. Sargent	WESTERN PENNSYLVANIA
John L. Calene	SOUTH DAKOTA
William C. Chaney	TENNESSEE
Louis E. Viko	UTAH
*C. C. Hillman	U. S. ARMY
*F. L. McDaniel	U. S. NAVY
*George Baehr	U. S. PUBLIC HEALTH SERVICE

. . . Chairman Cocke at this point introduced President Roger I. Lee. . . .

DR. ROGER I. LEE: Mr. Chairman, members of the Board of Governors: I have only a very short theme. That theme is one I have had for some time concerning the functions of the Governors of this College. I hope as the College grows, which it is doing, and as it acquires vitality, which it is doing, it will become more democratic and that the Governors will slowly acquire a great deal more influence in the affairs of the College. Events in the College the last few years, particularly the development of its graduate courses and of its regional meetings, have indicated very clearly that the Governors are by process of evolution and by process of discussion acquiring more and more influence in the shaping of the policies of the College. That is an excellent feature and as far as I have any influence, I shall support it. That can be carried very much farther, very likely not all at once, but it is a healthy and wholesome growth. . . . We want the College to be a democratic institution in a democratic country. (Applause)

CHAIRMAN COCKE: Gentlemen, we have lost one of our distinguished members by death, Dr. LeRoy S. Peters of Albuquerque, College Governor for New Mexico. Proper notice was taken by your Chairman, who communicated with Mrs. Peters, expressing our deep sympathy. At this meeting a successor will be elected.

We shall now hear the reading of the abstracted minutes of the last meetings of this Board at Boston in 1941.

. . . The Secretary read an abstract of the minutes of the two meetings in Boston in 1941 and these abstracts were approved as read. . . .

CHAIRMAN COCKE: Are there any communications, Mr. Secretary?

SECRETARY LOVELAND: I have none.

CHAIRMAN COCKE: The next item on the agenda will be a report from the Executive Secretary, Mr. Loveland.

SECRETARY LOVELAND: In line with our usual custom of keeping the Governors individually and as a whole advised and informed of happenings in the College, we have prepared for you, first, a list of all the candidates who have been acted upon by the Credentials Committee and the Board of Regents at the March and April meetings of this year. Notifications were sent to all Governors of the elections that took place during December, 1941. The first group of names placed in your hands is that of candidates recommended for election by the Credentials Committee at a meeting on March 22, 1942, this list in the meantime having been approved by the Board of Regents. The second list is a group which was recommended for election by the Credentials Committee on April 19, 1942, and which likewise has now been approved by the Board of Regents.

I have also placed in your hands a sheet, entitled "Term of Associateship Expired." There are seven Associates who have failed to qualify for Fellowship in their maximum five-year term and under the By-Laws their names must now be dropped.

Since the last annual session of the College, we have lost by death 48 Fellows, 5 Associates—Total, 53. This is about the average loss by death annually in the last few years.

Since the last session of the College, we have added 16 Life Members, making a grand total of 183, of whom 17 are now deceased, leaving 166.

Additions by election include 137 Fellows and 100 Associates on December 15, 1941, and 165 Fellows and 121 Associates on April 19, 1942, or a grand total of 523. Most of the new Fellows have been advanced from Associateship. There is a small shrinkage at the present time in the number of Associate candidates. This will have some direct effect on the number of advancements to Fellowship in subsequent years. The College membership is not materially increasing. There are numerous losses by death, and the net increase in membership actually is about 150 to 175 per annum. This is as intended by your Board of Regents, which has gauged the standards of admission accordingly.

I have also placed in your hands, for your information, the financial statements of the College for 1941. These statements have been audited by a certified public accountant. All details are given for those who are interested.

CHAIRMAN COCKE: Dr. Edward L. Bortz, Chairman, will now give the report of the Advisory Committee on Postgraduate Courses, the other members of this Committee being Drs. James J. Waring, Fred M. Smith, Ernest H. Falconer, and C. Sidney Burwell.

DR. BORTZ: Mr. Chairman, Members of the Board of Governors: After this Committee was appointed a year ago, it held a meeting and decided it would be advisable to offer approximately eleven postgraduate courses for the following year. With that in mind, overtures were made to certain outstanding clinicians throughout the country and satisfactory courses were arranged. With the national emergency that developed soon after December 7, 1941, the complexion of the postgraduate courses changed very radically and it was found expedient, because of the location of courses, or because of the involvement of large numbers of men who were on the faculties, or because of the lack of interest of members, to withdraw some of the courses. Even so, with the six courses that were given—one in Boston, one in New York City, one in Philadelphia, one in Minneapolis, and two in Rochester, Minn.—the total number of Fellows and Associates who took these courses equalled the number of registrants taking the courses a year earlier. A year ago there were 228: this year, 226. Had all the courses been given this year and had there not been a national emergency, the number of registrants, we believe, would have been well over 300. In view of the adverse conditions which existed, we feel that this year's program was a notable success.

We have talked with individuals who have been in attendance at all of the various courses this year and there have been not only commendation but expressions of approval in the most lavish terms, appreciation on the part of these student physicians for the high quality and intensive training that they have obtained through the College.

It was my privilege during the last few days to be in Rochester and to listen to the course on cardiovascular diseases given by Dr. E. V. Allen. I want to say that in my mind it would be impossible to conceive of a course better balanced, more expertly executed by highly qualified teachers of national renown who constituted that faculty. We must keep in mind that the College must accept its responsibility in carrying on the courses, and we do not know what the future has yet to offer, but we hope to carry on. Thank you. (Applause)

CHAIRMAN COCKE: Thank you, Dr. Bortz. I know we all appreciate the excellent work of the Committee. We have one of the Governors here who took one of the courses, and I am sure you would like to hear briefly from him. Dr. Lewis B. Flinn of Wilmington, Delaware.

DR. FLINN: Thank you, Mr. Chairman. I attended the course in Rochester which Dr. Bortz referred to, and I can do no more than to endorse all the remarks that he made about it. I can think of no way that such a course could be improved upon, and I am sure that it was the unanimous opinion of all those fifty men who were there that the time spent was more than worth while.

DR. ALLEN: It would only be fitting to say that if our course was a success, it was due to the fact that we had a good deal of help from the outside. About the time we had run out of ammunition, we were fortunate in having Dr. Roy Scott from Cleveland, Dr. Irvine Page from the University of Indiana, Dr. Roger I. Lee from Boston, and a number of others whom we were much pleased to have address us as guests. They were just the element that gave the punch to make it seem to us like a reasonably satisfactory course.

CHAIRMAN COCKE: Gentlemen, I think we have a very fine showing of attendance by the Governors or their alternates. Dr. M. C. Pincoffs, Editor of the Annals, has told me that even though he is in military service his Assistant Editor, Dr. Paul Clough, will carry on. In spite of all of these terrible times, we should not relinquish any of our activities or interests in the College. I think the feeling of the Board of Regents of the College is that activity should go on until such time as changes may become necessary.

Is there any new business?

DR. C. W. DOWDEN: I should like to bring up a matter I have had on my mind for some time. If you will look at your Program, you will find at the top of Page 5, "Qualified physicians who may wish to attend this Session as visitors; such physicians shall pay a registration fee of $12 and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee."

In the neighboring city of Minneapolis, we have meetings known as "The Young Men's Clinical Association" or some such name, comprised of young men under the age of thirty-five, who will probably make a considerable portion of the future membership of this College. Most of them are engaged in research work or in teaching. I understand that they can visit this meeting only upon payment of a $12 registration fee. Most of them have access to the ANNALS. One of our Louisville members has expressed himself as being opposed to this sort of thing. Then, too, there are other physicians, surgeons, who would like to attend these meetings, and they also have access to the ANNALS. These men say they often learn more at our meetings than they do at the surgical meetings and yet they must pay $12 to register. We have within one hundred miles a big clinic in which a relatively small percentage of the men are members of this College. They, too, have access to the ANNALS and yet they must pay, I understand, a registration fee of $12. I think that the College is too big for that. It seems to me this is a subject that can be discussed and we might thereafter approve of some plan. The main criticism is going to be the lack of facilities to take care of guests. That would have to be worked out. Certainly, in our general sessions, we can accommodate them. In our hospitals and clinics some plan would have to be devised. It does not seem quite right to me that this sort of thing should go on without something being done about it.

CHAIRMAN COCKE: There can be considerable clarification by the Executive Secretary, who will add some light to this before we open it for discussion.

SECRETARY LOVELAND: Dr. Dowden is correct in one of his assumptions, that this rule was adopted at a time when our members became somewhat annoyed with non-members taking up the places at the clinics. The present regulation was adopted by the Regents twelve years ago at our Minneapolis meeting. It was then pointed out that a great many physicians expressed the opinion that there was no need to join the College because they could take advantage of its meetings for nothing, whereas they would have to pay dues if they were members.

There is one impression I should like to correct. Any member of the College, who communicates with my office and states that he has a close friend or an assistant working with him whom he would like to bring to the meeting, is sent a courtesy card with an invitation for that doctor to come as a guest. Dr. Allen of the Mayo Clinic can tell you that we issued formal invitations to all graduate students from that institution to come to this meeting as guests. This was also done in connection with the University of Minnesota and in connection with the members of the Ramsey County Medical Society and the Hennepin County Medical Society.

The reason the $12 registration fee was selected was because the Associate dues in the College are $12. At the time the rule was adopted the annual sessions were the chief activities of the College. The Regents felt that someone outside the College ought to be willing to pay as much as an Associate for the benefit of attendance. There is no desire on the part of the College to collect money from guest physicians; the object is to protect our membership, assuring them of accommodation at all features on the program. You probably do not realize the difficulty we often experience in providing accommodations for our members alone, not only at clinics and panel discussions, but even to secure hotel accommodations. At our St. Paul session we shall have no difficulty with the panel discussions because the rooms are large, but this is not always so or possible.

DR. DOWDEN: Mr. Loveland, isn't there some plan that might be worked out—a plan that would take care of just such problems as we have been discussing? Of course, I do not mean to throw our meetings open to the whole medical field.

SECRETARY LOVELAND: It is certainly worthy of consideration. Whatever can be done without reducing seriously the facilities to our members would be appropriate.

CHAIRMAN COCKE: Would anyone else like to speak?

DR. GRIFFITH: Mr. Chairman, I agree with Dr. Dowden in regard to the charge. If we are going to make a charge, and we charge Associates $12 a year dues, we could open up our postgraduate courses to these registrants who want also to attend our annual meetings. In our meetings in Kansas City of the Southwest Clinical Society we charge those who wish to attend just half of what the regular fee for membership is. That holds down to a certain extent the number of attendants that would come if everything were free. We do, as Mr. Loveland said, have to protect our members. I do not think we should eliminate a registration fee, but it might be all right to reduce it.

CHAIRMAN COCKE: I will say for the benefit of certain of these postgraduate courses that have not been fully subscribed, that they have been filled in by nonmembers of the College under certain situations, so that it is a rather flexible arrangement, but the crux of the situation seems to concern whether the men should be allowed also to come to the annual sessions and pay a nominal registration fee rather than the present fee of $12. The present arrangement was a self-protective measure that became necessary in the past.

DR. IRVING S. WRIGHT: Just to have it on the record, I attended the American Federation for Clinical Research and the President announced at that time that inasmuch as they would meet in different parts of the country, there was no fixed policy to meet at the time of the American College of Physicians session. Therefore, if this came up for special consideration, that might be borne in mind.

CHAIRMAN COCKE: Gentlemen, I would say that this situation was taken into consideration by the Board of Regents last year and it was understood that the Federation would not regularly meet in conjunction with the College. However, it has been brought out that the College would extend every courtesy to the members of that Federation when it held its meeting in proximity to that of the College. Mr. Loveland tells me that this year the courtesy of attending our meeting was extended to them.

DR. RUSSELL: To cover the ground, might we not revise the announcement in the Program, stating that the $12 registration fee will be charged to qualified physicians "except those specifically invited." Let there be a clear understanding of the application of the registration fee and let it be known that any person who seems particularly desirable and whom a member wants to bring along, shall receive an invitation.

CHAIRMAN COCKE: That is, within the bounds of propriety.

DR. YATER: I second that.

CHAIRMAN COCKE: We can trust to the diplomatic phraseology of our Executive Secretary to fix up the announcement as it should be. Is there any other discussion? Are you ready for the question?

. . . There was no further discussion. The question was called and the motion carried. . . .

DR. STRONG: Mr. Chairman, I should like to bring a matter to the attention of this Board. I come from Vancouver, British Columbia, out on the edge of the continent. A matter has come to my attention several times and was brought again to my attention today by a member from that area. It is in regard to the notices of our meetings—for instance, the notices that carry with them the selection of clinics, panel discussions, etc., as well as the notices for the postgraduate courses. These notices are sent from the headquarters in Philadelphia by ordinary mail. They reach Vancouver in four or five days and obviously the notices mailed to members closer to Philadelphia have long since been delivered. This places members at far-away points at a disadvantage in registering for postgraduate courses, for clinics or panels, and by the time their applications arrive the capacities are often exhausted. In the interest of equity, would it not be possible to fix some scheme of zoning the country so that these notices may be delivered in a more equitable fashion? Even if our members in our location reply promptly, the applications will reach Philadelphia after many of the men from the more populous districts have replied. The central office of the College naturally makes reservations as received.

CHAIRMAN COCKE: Dr. Strong's remarks are quite in order, and we should like to hear from the Executive Secretary as to the possibility of correction, because certainly it is not the desire or the intention to make any distinction whatsoever and no one should be deprived by reason of geography of his choice of clinics.

SECRETARY LOVELAND: Dr. Strong is essentially correct. This condition did not hold this year in regard to clinics or panels at our St. Paul meeting, but this was because our facilities are practically unlimited. However, it might readily have occurred in regard to some of the postgraduate courses. I think Dr. Strong's request is reasonable and the situation can well be remedied. I will say, however, that as a matter of practice, we have always released mailings to the West Coast before those to the points nearer to Philadelphia, but possibly we did not allow enough time between the two groups. The central office will carefully gauge the time of mailings in the future.

DR. BORTZ: Mr. Chairman, owing to the present national emergency, a situation has arisen that never confronted this body before. I am asked to bring to the attention of the Board the problem of those Governors who are going into military service and who, therefore, will be away from their natural place of residence. For instance, Dr. Charles E. Watts, Governor for Washington, is now on active duty in San Diego. His term of office terminates this year, but in all likelihood the Committee on Nominations will again choose to nominate him for that important office. There may be many others involved. Now, should these men resign from their positions as Governors of their particular states or territories, or should the men confer with the Executive Committee, or with the Regents, or with the President, and have an Acting Governor appointed to act for them, or just what is the solution? I present this for discussion.

CHAIRMAN COCKE: I will say, Gentlemen, that the matter has been brought to my attention only in one instance, the case of Dr. Drake, Governor for Maine. However, he stated his duties would not take him more than sixty miles from his home, and while he would have time to attend to his duties as Governor, he was willing to resign. I requested him, certainly until this meeting, that since he would not be out of touch either geographically or otherwise with his duties, to continue if he had available time to function as Governor. Dr. Drake, will you speak for yourself?

DR. DRAKE: I have not been able to live in my own locality right along, but I have been there frequently and nothing, such as proposals of membership and other matters, has come up that I could not handle.

DR. DOWDEN: I have one other matter which I am sure Mr. Loveland can clarify for me. We have in our section one young man who has just finished his Associateship. He is in the Army. He won't have time to get his case records ready to qualify. He is taking his examination in the American Board today. He wonders what his status will be in case he passes his examination or in case he does not have time to prepare his case histories.

CHAIRMAN COCKE: The Regents are going to be very lenient in this situation—that is, when a man is in military service and deprived of opportunities to meet the requirements. You may tell him that some provision will be made. I don't know just exactly what it will be, but the Regents have discussed it.

DR. CASON: I would like to move that the Board of Governors go on record requesting that no change be made that would not otherwise be made in the status of men either in the service or contemplating entering the service, and wherever it is requested by the Governor, that an Acting Governor be appointed until his return to his state.

DR. KERR: I second the motion.

DR. DOWDEN: Could that be amended to include not only the Governors but men coming up for their final examination or advancement?

CHAIRMAN COCKE: That should be a separate motion.

DR. CASON: Let's keep this straight.

SECRETARY LOVELAND: There is a special consideration in the matter of an Acting Governor. If a Governor of the College is on active military duty where he cannot be reached by the men in his state, the situation naturally would shut off all candidates from that state. We have had this experience for the first time this year. We had a new Governor for Panama and the Canal Zone. He left the Canal Zone but did not resign, and in addition, we were unable to contact him a part of the time. His address was changed two or three times. We had two candidates from the Canal Zone, Associates who wanted to come up for Fellowship, and under the By-Laws they could not come up for consideration because there was no one available to endorse them. We must have the machinery for an Acting Governor or someone to endorse a candidate if the regular Governor is on active duty at considerable distance.

DR. CASON: This was my idea, and I am asking that an alternate or Acting Governor be appointed to do that.

SECRETARY LOVELAND: Mr. Chairman, the resolution authorizing the appointment of an alternate Governor applies only to alternates to attend the annual meetings of the College. That provision was made a few years ago, and the alternate has only that authority.

DR. CASON: Could we then, as part of this motion, put in that the Board of Regents be authorized or requested to adopt a resolution authorizing the alternates in this emergency to have the additional authority to endorse candidates and perform other duties ordinarily required of the regular Governor?

. . . This alteration to the motion was agreeable to the seconder. . . .

DR. BORTZ: Because of the important work that the Governors have to carry on, might it not be wise and resourceful to consider at least the advisability of having one or even two or three alternates to the Governor as an established policy? There are, for example, many delegates to the House of Delegates of the A. M. A. and alternate delegates from the different sections of the country. Also, in many states there are delegates from the state medical societies, and these delegates, I believe, also have alternates. We have over 3,500 Fellows, and we would certainly have a sufficient number to have one or two alternates to the Governor in each state. There are many possibilities arising, such as moving from one locality to another, death, or unforeseen situations which might leave a Governor's area without representation, and it would seem to me at this time very helpful if at least one alternate or possibly a first and second alternate to a Governor be appointed for all of the different Governors' areas.

CHAIRMAN COCKE: Your remarks have been very interesting and worth while, but we are confronted with the By-Laws, and the By-Laws are something the Regents cannot change. It states here, Article IV, Section 1, Paragraph Five:

> "Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session. Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed. The same alternate shall not be appointed for more than two consecutive years."

The Board of Regents has no authority to change the By-Laws except by the necessary legal method. Any proposal has to lie on the table and be published some thirty days before the annual meeting.

SECRETARY LOVELAND: An amendment to the By-Laws of the College must be submitted in writing to the Board of Regents at least thirty days before any annual meeting of the Members of the College.

DR. SLOAN: Is there not some machinery which operates in this society in this emergency? If a Governor dies, what happens?

CHAIRMAN COCKE: The President may appoint a Governor until the next regular election.

DR. SLOAN: Would that not cover this situation?

CHAIRMAN COCKE: I think it could, through the coöperation of the Governor.

DR. SLOAN: Is there a possibility of granting a leave of absence and appointing an Acting Governor?

CHAIRMAN COCKE: I think the Executive Committee, which has power to function in any emergency, might do that.

DR. CASON: Isn't that what you would be doing under my motion?

DR. WARING: There are several problems involved here. In the first place, there is some confusion because of the use of the word "alternate" for the Governor. In the second place, some provision must be made about the old Governor, the one who goes into service and is no longer able to function on account of non-residence in his territory. Are we going to ask this man to resign or will he voluntarily do so? Or will someone be appointed in his place until he does resign? Some action ought to be taken, perhaps by correspondence with the Executive Office or the Governor, pointing out to that man that if he does go into service and the affairs of the College can no longer he attended to by his office, that he kindly notify the Executive Office so that the Executive Committee may appoint another in his place. I understand that the Executive Committee has the authority to appoint someone in his place, and it seems to me it might be left to the Executive Committee whether or not somebody should be appointed temporarily or permanently in his place.

CHAIRMAN COCKE: As I understand the By-Laws, the President has power of appointment only in case of resignation or death. I think we could get around this by a slight change in phraseology, using some such word as "substitute" Governor. Whether that would be any different from "alternate" I don't know. Outside of suggesting to the Board of Regents, I don't think we can approach this matter with any finality. The Regents will be guided largely by our suggestions.

DR. BURGESS: Mr. Chairman, I would like to suggest to Dr. Cason that he use in his motion "Acting Governor."

DR. ALLEN: There have been so many good ideas that it seems too bad to be in too big a hurry. While we ought to consider the national emergency, it seems more possible for the Chairman to appoint a small committee to give this thorough consideration with the ideas that have been expressed here. However, there is a motion before the House.

. . . CHAIRMAN COCKE presented the motion and it was carried. . . .

DR. KRAUSE: Frequently I have heard the desire expressed for information as to the proceedings in our panel discussions. I wonder if there are any facilities by which notes could be printed and distributed to members who are unable to attend. The panels are so small so far as the number they accommodate is concerned, and so very interesting and worth while, that many members have asked if they can obtain proceedings thereof.

CHAIRMAN COCKE: At this meeting the panel accommodations are unusually adequate. Have any been over-subscribed?

SECRETARY LOVELAND: No.

CHAIRMAN COCKE: The smallest panel room this year accommodates 175 and the larger rooms are unlimited.

DR. KRAUSE: But there are several panels going on simultaneously and a member can attend only one at a time.

CHAIRMAN COCKE: The only solution would be the employment of professional reporters, which would be a considerable expense. How that expense could be apportioned would be difficult.

SECRETARY LOVELAND: The transcription and distribution of panel discussions have received very careful study in former years. We investigated the cost of employing reporters and making transcripts and then mimeographing enough copies not only for those who attended the panels, but for anyone who desired copies. We found that for a single Session this cost would amount to from $2,500 to $5,000.

CHAIRMAN COCKE: I agree with Dr. Krause that proceedings of the panels would be desirable except for the cost. I myself have had to attend so many meetings that I have been deprived of many valuable panels.

. . . CHAIRMAN COCKE then read several announcements and declared the meeting adjourned, at 6:20 p.m.

Attest: (Signed) E. R. LOVELAND,
Secretary

MINUTES OF THE BOARD OF GOVERNORS

ST. PAUL, MINN.

April 22, 1942

The second meeting of the Board of Governors, in conjunction with the Twenty-sixth Annual Session of the American College of Physicians, convened in the Municipal Auditorium, St. Paul, Minn., Wednesday, April 22, 1942, at 12 noon, Chairman Charles H. Cocke presiding and Executive Secretary E. R. Loveland acting as Secretary, and with the following members or their alternates in attendance.

Oliver C. Melson	ARKANSAS
Ernest H. Falconer	NORTHERN CALIFORNIA
*Edgar Hull	LOUISIANA
Henry R. Carstens	MICHIGAN
Edgar V. Allen	MINNESOTA
*Graham Asher	MISSOURI
*Harry T. French	NEW HAMPSHIRE
George H. Lathrope	NEW JERSEY
Charles H. Cocke	NORTH CAROLINA
*L. H. Fredericks	NORTH DAKOTA
Alexander M. Burgess	RHODE ISLAND
*L. E. Madden	SOUTH CAROLINA
Paul K. French	VERMONT
Walter B. Martin	VIRGINIA
*E. G. Bannick	WASHINGTON
Albert H. Hoge	WEST VIRGINIA
Charles F. Moffatt	QUEBEC
*J. H. Watkins	ALABAMA
Fred G. Holmes	ARIZONA
Lewis B. Flinn	DELAWARE
Turner Z. Cason	FLORIDA
Charles Henry Sprague	IDAHO
LeRoy H. Sloan	NORTHERN ILLINOIS
C. W. Dowden	KENTUCKY
Eugene H. Drake	MAINE
Louis Krause	MARYLAND
John G. Archer	MISSISSIPPI
Ernest D. Hitchcock	MONTANA
*Irving S. Wright	EASTERN NEW YORK
A. B. Brower	OHIO
Homer P. Rush	OREGON
M. D. Levy	TEXAS
Elmer L. Sevringhaus	WISCONSIN
Ramon M. Saurez	PUERTO RICO
George F. Strong	ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN
Roy E. Thomas	SOUTHERN CALIFORNIA
James J. Waring	COLORADO
*J. S. Nickum	CONNECTICUT
Wallace M. Yater	DISTRICT OF COLUMBIA
Cecil M. Jack	SOUTHERN ILLINOIS
Robert M. Moore	INDIANA

Harold H. Jones	KANSAS
William B. Breed	MASSACHUSETTS
Warren Thompson	NEBRASKA
Nelson G. Russell, Sr.	WESTERN NEW YORK
Leander A. Riely	OKLAHOMA
*L. D. Sargent	WESTERN PENNSYLVANIA
John L. Calene	SOUTH DAKOTA
William C. Chaney	TENNESSEE
Louis E. Viko	UTAH
Warren S. Lyman	ONTARIO
*C. C. Hillman	U. S. ARMY
*F. L. McDaniel	U. S. NAVY
*George Baehr	U. S. PUBLIC HEALTH SERVICE

CHAIRMAN COCKE: I have the privilege of presenting the President-Elect, Dr. Paullin.

PRESIDENT-ELECT PAULLIN: Members of the Board of Governors, it would not be possible for me at the present time, with conditions as they are, to assume the responsibilities that naturally would fall on my shoulders as the incoming President of this Organization unless I felt and knew that I had such a group of men qualified to help carry on the duties and responsibilities of this organization. To you, it is a great responsibility, and I look forward with the greatest of pleasure to your coöperation and help in maintaining the high ideals and standards for which this College stands. During the past year it has been my pleasure by mail to contact most of you in this arduous task which the College assumes in the responsibility of aiding the armed forces. Through your help and that of others, it has been possible to provide this service for the Surgeons General of the Army and Navy. For this we are very grateful, because this work is not only most valuable to them, but it has been of the greatest usefulness from the standpoint of helping the medical profession. We have attempted, through your hearty coöperation, to keep square pegs out of round holes, and we have tried to make available for the personnel of the Army and Navy the qualifications of the physicians so that these doctors would give their greatest opportunity of service to this country in this extremely important time. For your coöperation and for your help I am indeed most grateful and I know that I can continue to expect it in the year that is before us. Thank you. (Applause)

CHAIRMAN COCKE: The Secretary will now read the abstract of minutes of our preceding meeting.

. . . Secretary Loveland read the abstract of minutes of the meeting of Monday, April 20, 1942. . . .

CHAIRMAN COCKE: I shall now report from the Board of Regents the following resolutions:

1. By resolution the Board of Regents on April 21 provided that all Fellows and Associates of the College on full-time active military service, whether in the regular or reserve Medical Corps, shall from January 1, 1942, have full remission of dues, it being provided that such members shall inform the Executive Offices of the College of the date upon entry into active service and also the date of retirement from active duty. The resolution further provided that the initial fee for such men shall be reduced to $10.00.

2. By another resolution the Board of Regents provided that any member of the Board of Governors called to active military service, thereby being unable to perform his duties as Governor, may temporarily be relieved by an Acting Governor appointed by the Executive Committee, due consideration to be given to any nomination or nominations made by the Governor who can not serve.

I might also add that at this meeting, upon the suggestion of Dr. Ernest E. Irons, Chairman of the American Board of Internal Medicine, it was proposed that fees for the Board examination may be reduced from $50.00 to $40.00 and that the Fellowship initiation fee in the College may be reduced from $80.00 to $65.00, these reductions to apply to elections after January 1, 1943. Therefore, what formerly cost men a total of $130.00 for Fellowship in the College and certification by the Board will be reduced to $105.00. I think the Regents have met your request in a very fine way. Has anyone anything he would care to say about this matter? If not, we will proceed with reports.

Are there any committees that have not previously reported that would like to make a report now? Unfortunately, Dr. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, has to attend a Panel Discussion and he may be delayed in getting here.

There is the matter of the reappointment of the Advisory Committee on Postgraduate Courses. I take great pleasure in reappointing the exact committee which has functioned so admirably this year, consisting of Dr. Bortz, Chairman, Dr. James J. Waring, Dr. Fred M. Smith, Dr. Ernest H. Falconer, and Dr. C. Sidney Burwell.

We are now ready for new business.

DR. MELSON: Mr. Chairman, members of the Board of Governors, it seems to be a law of nature that loss is balanced by gain. As you know, our General Chairman is going to be elevated to the position of Vice President of this College and we are to lose a very valuable instructor and his happy presiding qualities. I rise to move that a resolution from the Board of Governors be submitted to the Board of Regents that a gavel be presented to Chairman Cocke on behalf of the Board of Governors from the College.

. . . Vice Chairman Dowden assumed the chair. . . .

DR. BREED: I second Dr. Melson's motion.

. . . Vice Chairman Dowden presented the motion, which was unanimously carried, whereupon Chairman Cocke resumed the chair. . . . (Applause)

CHAIRMAN COCKE: Gentlemen, I really cannot tell you with what sincere appreciation I feel this distinguished honor. During my years of association with you, and I have been on this Board twelve or thirteen years with a fair proportion of them as your Chairman, I have met not only with your constant courtesy and loyal cooperation, but also with your very faithful and interested attendance at the meetings. This meeting is probably the largest, and to have such a gathering at such times as these is most gratifying. I feel that the spirit of this Board of Governors is going to carry on and add more and more to the advancement of this College, which we think has such a worthwhile destiny. I thank you deeply. (Applause)

DR. BROWER: Mr. Chairman, recognizing that we must lose you as Chairman, I suppose it is in good form to consider the incoming Chairman. I have in mind a man who has served on many important committees, he has always had the deepest interest of the College at heart, a man who last year helped to make the meeting in Boston probably one of the best we have ever had. It gives me pleasure, Gentlemen, to nominate Dr. William B. Breed of Boston as Chairman of this Board of Governors for a term of three years.

DR. LATHROPE: I second the nomination. I have been a member of this Board only two or three years. The pace that Dr. Cocke has set as Chairman has been a pretty good one as has just been testified to. You saw what a grand job was done by the gentleman from Massachusetts a year ago. We all know his personality, and I know no one who would be better qualified or better able to keep up to the current that has already been set.

CHAIRMAN COCKE: Do I hear other nominations?

DR. DOWDEN: Mr. Chairman, I move that nominations be closed and the Secretary cast the ballot for Dr. Breed.

. . . Chairman Cocke called the question and the motion was unanimously carried, and the Secretary cast the ballot for Dr. Breed's election. . . .

DR. BREED: Gentlemen, I appreciate the confidence you have placed in me by making me Chairman of this Board. I cannot predict what this Board will be like without Dr. Cocke. He has been Chairman ever since I have been on the Board, and I do not see how anybody could keep the pace Dr. Cocke has set.

CHAIRMAN COCKE: There is another important office—not an office but a position to be filled, which is the function of this Board, and that is a membership on the Credentials Committee. Needless to say, this requires continuity of service and experience. Dr. J. O. Manier's term expires at this meeting. He is eligible for reappointment if desired. I should like to hear suggestions as to whom the Board desires to appoint.

DR. DOWDEN: I move, Mr. Chairman, that Dr. Manier be reappointed.

DR. LATHROPE: I second the nomination.

CHAIRMAN COCKE: Do I hear other nominations? All those in favor of Dr. Dowden's motion will signify by saying aye; opposed, no.

. . . The motion was unanimously carried. . . .

CHAIRMAN COCKE: That appointment is for three years. This Committee is constantly renewed or appointed and it has a fair degree of continuity. My own term of service on the Committee is not the problem of this Board but that of the Board of Regents. It expires this year.

SECRETARY LOVELAND: The Board of Governors, however, must appoint another member on the Committee on Credentials to fill out the unexpired term of the Chairman, because Dr. Cocke's retirement from the Board of Governors creates a vacancy. The Board of Governors appoints three members of this Committee as does also the Board of Regents. I feel sure the Board of Regents will want to retain Dr. Cocke's services on the Credentials Committee, but if so, his appointment will be from among those selected by the Board of Regents.

DR. RUSSELL: I would like to nominate Dr. Wallace M. Yater.

DR. DOWDEN: I second the motion.

CHAIRMAN COCKE: Do I hear other nominations?

. . . There were no further nominations. The question was called and the motion was carried. . . .

CHAIRMAN COCKE: This appointment is for two years, until 1944.

. . . Dr. Nelson G. Russell, Sr., Governor for Western New York, opened a discussion concerning the requirements for advancement to Fellowship insofar as certification by the American Board of Internal Medicine was concerned. It was clearly revealed that all Associates elected since April 6, 1940, shall present as one of the professional prerequisites for advancement to Fellowship certification by the American Board of Internal Medicine or by the certifying board in any of the allied specialties, with the exception that such certification shall not be required of candidates from the Army and Navy and Public Health Services, nor of candidates in whose specialty there exists no certifying board. . . . Following this there was widespread discussion, in which various members of the Board of Governors joined, concerning qualifications for membership in the College and concerning the examinations conducted by the American Board of Internal Medicine. Out of this discussion there came certain suggestions concerning the type of examinations, both written and oral, which are now being given and the recommendation that an effort be made to encourage all applicants to take the examinations for entrance into the College, but that the Board of Regents of the College be requested to inquire into the present workings of the examining board and possibly to recommend that the type of examination should differ from the ordinary academic examination and be a more comprehensive test of the clinical knowledge of the applicants in handling patients, as well as contain some theoretical questions relating to problems which have very little or no clinical significance. . . .

DR. WARING: Mr. Chairman, I should like to bring up for discussion a matter relating to the interpretation of the essential work carried on by the industrial hygiene clinics by the induction of important members thereof into the military service. At present the Army and Navy have directly under their supervision the manufacture of munitions for the war services, and in both of these organizations and in particular companies involved, the Army and Navy have deferred the doctors and the important assistants in their laboratories from induction into the armed forces. At the present time members of the state boards of health are automatically members of the U. S. Public Health Service, as I understand it, and all of their laboratory assistants are deferred in order that the health of the people in the various states may be protected. But, this protection has not extended, up to the present time, to the industrial hygiene clinics, heads of those clinics, and their laboratory assistants in industry. This is a very important matter.

In the Colorado University School of Medicine there is a Division of Industrial Hygiene and the man at the head of this has had a nation-wide opportunity to render very important service to industry and the protection of employees of industry against occupational diseases. Under the pressure of the present emergency all of these industries are trying desperately to produce military supplies as rapidly as possible. The methods that have been put into effect in manufacturing these munitions have not in every case succeeded in protecting many employees against occupational diseases such as lead poisoning, metallic poisoning, dust in the lungs, etc. In Colorado this matter of dust in the lungs is extremely important. The man who is head of our industrial division of hygiene has set up industrial clinics in various parts of the country. In many of these clinics work has been disrupted by the removal of the doctor in charge. In one important clinic the work was disrupted by the removal of the doctor and the technical assistant. The same thing has applied to the Colorado Mining Company at Pueblo, the same to the industrial hygiene clinics in various subsidiary companies—The American Brake Shoe & Foundry Company and others. At the present time the Army and Navy protects its own industrial hygiene plants. The State Board of Health and the people are protected, and the people in industry are not protected.

It is extremely difficult to replace these doctors who are removed from these industrial and hygiene clinics and it is much more difficult to replace their technical assistants, who are also being removed and taken into the service. This same thing applies to many other occupations besides those immediately concerned in the medical profession. It applies to chemistry. I heard an important man talking over the radio from England recently. He spoke of the tragedy of putting important manpower into the expeditionary forces. He said he saw a man who had a national reputation as a chemist in America, serving in the forces. That is only an isolated instance, but I could name for you half a dozen or more specific instances of the same sort.

The American College of Physicians is going to have to recognize that situation and perhaps do what some other organizations have done. The American Chemical Society has pointed out the flaws in the induction of men to service and has gone on record protesting against the inefficient way that induction is handled.

I bring the matter up for discussion, Mr. Chairman. If you agree with me, I shall be glad to present a motion later.

CHAIRMAN COCKE: Let us have a little discussion. We have with us one who is intimately acquainted with the situation—Dr. Paullin.

DR. PAULLIN: I do not want to monopolize the time of this Board, but I think I can help Dr. Waring straighten out his problem very easily. The Procurement and Assignment Agency is a Federal agency. In each state of the Union there is appointed a chairman and in each co-area there is a co-area chairman. On this Board there are two physicians in general practice, one physician from the American Asso-

ciation of Medical Colleges, one member from the American Veterinary Association, and two dentists. This co-area committee and the state chairman work in coöperation with the Selective Service, Act Number 1 and Act Number 2.

In medical work, one is permitted to write out a list of his essential teachers in a particular department—an essential list of individuals who are necessary in these industrial plants. If these men are subject to Selective Service, they can be deferred by the local draft board after consultation with the state chairman or if they do not get satisfaction from the state chairman, they can appeal to the area committee, and if satisfaction is not obtained there, one can appeal to General Hershey. There is ample machinery to protect all of these men in any vital industry. All one has to do is to go to the state chairman and present his case—show the need and immediate advice will be sent to the local Selective Service Board, because this Board is required by Act of Congress to accept the recommendation of this Committee on Procurement and Assignment. The machinery is all there; all you have to do is to use it.

Of course, there is at present great difficulty in establishing standards for essential industry. When you realize the extreme need in the Army at present, it is easier to understand things. Furthermore, all of the needs of the country are paramount to every other thing. The country's needs come first, civilian needs are next, and it is going to be a difficult problem to establish a yardstick by which you can determine the essential need of any given industry or teaching unit or Public Health Service.

In so far as medical service is concerned, civilian needs, public health needs, and Army needs have got to be rationed and the greatest use made of the manpower that we have at our command. The requisitioning agencies that are constantly sending in requests for doctors do not seem to realize that there are only 189,000 physicians in the United States. I believe that the Office of Civilian Defense has full power to requisition the doctors they need. I am quite certain from observation and experience with the service for the past two years that it is functioning just as well as it possibly can.

DR. WARING: I am afraid Dr. Paullin misunderstood me somewhat. We are not concerned by interruption in the Medical School. It is not the young men in the industrial hygiene clinics nor the technical assistants; it is the young men who are constantly trained in carrying out certain essential technical procedures in the laboratories of these industrial hygiene clinics. Dr. Paullin has a much more optimistic view of the way it functions than I have. Mr. Cummings, who is in charge of hygiene at our medical school, tells me that during the past six months he has been called a dozen or more times a day. There is desperate need all over the country, and it is being constantly demanded that he furnish technical assistants who are being taken from the industrial hygiene clinics scattered over the country. There is not at the present time in the Office of Production Management any specific responsible person or committee that has the specific responsibility of taking care of this situation. It is looked after by the Army for the particular companies that are immediately under the management of the Army; it is taken care of by the Navy in the Navy Yard under the management of the Navy; it is being taken care of by the U. S. Public Health Service as far as the State Board of Health and all their technical assistants are concerned. It is absolutely not being taken care of so far as it relates to the industrial hygiene clinics, and that is absolutely true in the case of our experience in Colorado, and it must be true in many other instances all over the country.

CHAIRMAN COCKE: Col. Hillman, would you care to comment?

COL. C. C. HILLMAN: It would appear that Dr. Waring's chief concern is not about doctors but civilian technicians. As I see it, it would take it out of the Procurement and Assignment Bureau and put it into the Selective Service. I think the channels of relief should be sought through your State Selective Service organization, and if this State Selective Service does not feel competent or does not deem it advisable to act, one would have recourse to the National Selective Service Head-

quarters under General Hershey. This is just one of many similar examples. Just as a citation of something that came up a little while ago—there was a question of the manufacture of artificial limbs. The question concerned whether or not their technicians should be inducted. They thought there were not very many of this kind of technicians and that we are certainly going to need more artificial limbs and that, therefore, these technicians should be deferred. It came to the Surgeon General's office, up through Selective Service. I think it was acted favorably upon.

CHAIRMAN COCKE: Capt. McDaniel, would you care to comment?

CAPT. F. L. MCDANIEL: Mr. Chairman and Gentlemen: In the Navy the damage so far is not so bad. We are not using selectees. The Navy is a voluntary organization up to the present time and the District Commandant can either accept or reject the application for enrollment or enlistment or commission, so that we are not taken by force nor are we taking by force anyone from any private industry or from any vital spot. Of course, it may later come to that and the Navy may take selectees for the continuance of the war. In that case, I think we would handle it as Dr. Paullin has suggested, through the local draft boards and appeal to the central headquarters in Washington.

When I make my personal report to Admiral McIntire, I shall be glad to mention this to him, and I am sure that he is in a position to take it up at the proper places.

DR. WARING: I should like to make it perfectly clear that this problem does not apply solely to the 8th Corps Area because these industrial hygiene clinics that are served are scattered over the country. There are numerous Selective Service agencies that are concerned and not solely one agency.

DR. PAULLIN: I thought Dr. Waring was thinking of professional persons. I am sure Selective Service can help you with your technicians if you present your problems to it.

CHAIRMAN COCKE: The Chairman of the Advisory Committee on Postgraduate Courses has come in. Dr. Bortz, will you give us a report?

DR. BORTZ: Mr. Chairman, I reported on the postgraduate courses given this year at the preceding meeting of the Board of Governors, and following that we had a Committee meeting at which the members present were very positive in their ideas that we should carry on the work. A suggestion was made that we make plans for a course in general medicine in Boston, a course in allergy in New York, a course in general medicine in Philadelphia, a course in general medicine at the Mayo Clinic, and a course in internal medicine at the Continuation Center of the University of Minnesota, Minneapolis. The details concerning these courses, the dates, duration, etc. will have to be worked out in conjunction with the leaders of the courses. I have talked with representatives such as Dr. Robert Cooke of New York, men from Philadelphia, Dr. Allen of the Mayo Clinic, and with Dr. Watson at the University of Minnesota, and all have voiced deep interest and assured the College of their utmost coöperation in endeavoring to work out an adequate and satisfactory program for next year. Probably two courses will be offered in the early part of February and the other three courses will be pre-meeting courses.

. . . There were no further matters to be brought before the Board whereupon the meeting was adjourned at 2 p.m.

Attest: (Signed) E. R. LOVELAND,
Secretary